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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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AstraZeneca AB

151 85 Södertälje
SUEDE

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Chemical compounds

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CHEMICAL COMPOUNDS

The present invention relates to quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with angiogenesis and/or increased vascular permeability, to their use as medicaments and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals such as humans.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with in vitro endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844). Basic FGF (bFGF) is a potent stimulator of angiogenesis (e.g. Hayek et al, 1987, Biochem. Biophys. Res. Commun. 147: 876-880) and raised levels of FGFs have been found in the serum (Fujimoto et al, 1991, Biochem. Biophys. Res. Commun. 180: 386-392) and urine (Nguyen et al, 1993, J. Natl. Cancer. Inst. 85: 241-242) of patients with cancer.

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a

segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt-1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another fms-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1 and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

The present invention is based on the discovery of compounds that surprisingly inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, lymphoedema, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation.

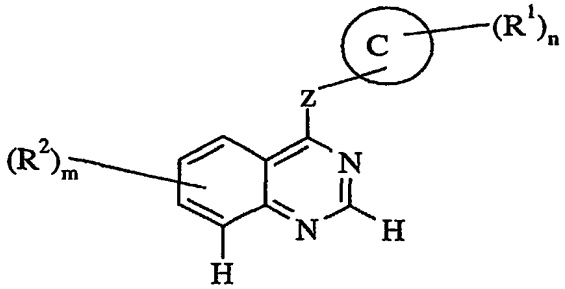
VEGF is a key stimulus for vasculogenesis and angiogenesis. This cytokine induces a vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration, and subsequent organisation of cells to form a capillary tube (Keck, P.J., Hauser, S.D., Krivi, G., Sanzo, K., Warren, T., Feder, J., and Connolly, D.T., Science (Washington DC), *246*: 1309-1312, 1989; Lamoreaux, W.J., Fitzgerald, M.E., Reiner, A., Hasty, K.A., and Charles, S.T., Microvasc. Res., *55*: 29-42, 1998; Pepper, M.S., Montesano, R., Mandroita, S.J., Orci, L. and Vassalli, J.D., Enzyme Protein, *49*: 138-162, 1996.). In addition, VEGF induces significant vascular permeability (Dvorak, H.F., Detmar, M., Claffey, K.P., Nagy, J.A., van de Water, L., and Senger, D.R., (Int. Arch. Allergy Immunol., *107*: 233-235, 1995; Bates, D.O., Heald, R.I., Curry, F.E. and Williams, B. J. Physiol. (Lond.), *533*: 263-272, 2001), promoting formation of a hyper-permeable, immature vascular network which is characteristic of pathological angiogenesis.

It has been shown that activation of KDR alone is sufficient to promote all of the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and survival, and the induction of vascular permeability (Meyer, M., Clauss, M., Lepple-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Büttner, M., Rziha, H-J., and Dehio, C., EMBO J., *18*: 363-374, 1999; Zeng, H., Sanyal, S. and Mukhopadhyay, D., J. Biol. Chem., *276*: 32714-32719, 2001; Gille, H., Kowalski, J., Li, B., LeCouter, J., Moffat, B, Zioncheck, T.F., Pelletier, N. and Ferrara, N., J. Biol. Chem., *276*: 3222-3230, 2001).

International patent application publication number WO 00/47212 describes VEGF receptor tyrosine kinase inhibitors. Compounds of WO 00/47212 possess activity against VEGF receptor tyrosine kinase (RTK) such that they may be used in an amount sufficient to inhibit VEGF RTK whilst demonstrating no significant activity against EGF RTK. Their VEGF RTK inhibitory activity is due both to activity against KDR and against Flt-1, but generally they are more potent against KDR. Generally they have extended plasma pharmacokinetics. Some VEGF RTK inhibitors have been found to act as potassium channel blockers and are positive in a hERG assay; such activity may give rise to ECG (electrocardiogram) changes *in vivo*. Compounds of WO 00/47212 have predominantly basic side chains.

Surprisingly we have now found compounds of the present invention to be very potent KDR inhibitors but to have less activity against Flt-1 than compounds of WO 00/47212, to have less extended plasma pharmacokinetics than compounds of WO 00/47212 and to be inactive or only weakly active in a hERG assay. Compounds of the present invention have predominantly neutral side chains.

According to one aspect of the present invention there is provided the use of a compound of the formula I:



(I)

wherein:

ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which moiety may be saturated or unsaturated, which may be aromatic or non-aromatic, and which optionally may contain 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH- or -S-;

n is 0, 1, 2, 3, 4 or 5;

m is 0, 1, 2 or 3;

R^2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl, $-NR^3R^4$ (wherein R^3 and R^4, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or R^5X^1- (wherein X^1 represents a direct bond, -O-, -CH_2-, -OC(O)-, -C(O)-, -S-, -SO-, -SO_2-, $-NR^6C(O)$-, $-C(O)NR^7$-, $-SO_2NR^8$-, $-NR^9SO_2$- or $-NR^{10}$- (wherein R^6, R^7, R^8, R^9 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^5 is selected from one of the following twenty-two groups:

1) hydrogen, oxiranylC_{1-4}alkyl or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) C_{1-5}alkyl$X^2C(O)R^{11}$ (wherein X^2 represents -O- or $-NR^{12}$- (in which R^{12} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{11} represents C_{1-3}alkyl, $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein R^{13}, R^{14} and R^{15} which may be the same or different each represents hydrogen, C_{1-5}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{16} (wherein X^3 represents -O-, -S-, -SO-, -SO_2-, -OC(O)-, $-NR^{17}C(O)$-, $-C(O)NR^{18}$-, $-SO_2NR^{19}$-, $-NR^{20}SO_2$- or $-NR^{21}$- (wherein R^{17}, R^{18}, R^{19}, R^{20} and R^{21} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group $-(-O-)_f(C_{1-4}alkyl)_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{22} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, $-SO_2-$, $-NR^{23}C(O)-$, $-C(O)NR^{24}-$, $-SO_2NR^{25}-$, $-NR^{26}SO_2-$ or $-NR^{27}-$ (wherein R^{23}, R^{24}, R^{25}, R^{26} and R^{27} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{22} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

5) R^{28} (wherein R^{28} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group $-(-O-)_f(C_{1-4}\text{alkyl})_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

6) C_{1-5}alkylR^{28} (wherein R^{28} is as defined hereinbefore);

7) C_{2-5}alkenylR^{28} (wherein R^{28} is as defined hereinbefore);

8) C_{2-5}alkynylR^{28} (wherein R^{28} is as defined hereinbefore);

9) R^{29} (wherein R^{29} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from oxo, hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $-C(O)NR^{30}R^{31}$, $-NR^{32}C(O)R^{33}$ (wherein R^{30}, R^{31}, R^{32} and R^{33}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and a group $-(-O-)_f(C_{1-4}\text{alkyl})_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

10) C_{1-5}alkylR^{29} (wherein R^{29} is as defined hereinbefore);

11) C_{2-5}alkenylR^{29} (wherein R^{29} is as defined hereinbefore);

12) C_{2-5}alkynylR^{29} (wherein R^{29} is as defined hereinbefore);

13) C_{1-5}alkylX^6R^{29} (wherein X^6 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{34}C(O)-$, $-C(O)NR^{35}-$, $-SO_2NR^{36}-$, $-NR^{37}SO_2-$ or $-NR^{38}-$ (wherein R^{34}, R^{35}, R^{36}, R^{37} and R^{38} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

14) C_{2-5}alkenylX^7R^{29} (wherein X^7 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{39}C(O)-$, $-C(O)NR^{40}-$, $-SO_2NR^{41}-$, $-NR^{42}SO_2-$ or $-NR^{43}-$ (wherein R^{39}, R^{40}, R^{41}, R^{42} and R^{43} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

15) C_{2-5}alkynylX^8R^{29} (wherein X^8 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{44}C(O)-$, $-C(O)NR^{45}-$, $-SO_2NR^{46}-$, $-NR^{47}SO_2-$ or $-NR^{48}-$ (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

16) C_{1-4}alkylX^9C_{1-4}alkylR^{29} (wherein X^9 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{49}C(O)-$, $-C(O)NR^{50}-$, $-SO_2NR^{51}-$, $-NR^{52}SO_2-$ or $-NR^{53}-$ (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined hereinbefore);

17) C_{1-4}alkylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore);

21) C_{2-5}alkynylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined hereinbefore); and

22) C_{1-4}alkyl$R^{54}(C_{1-4}$alkyl$)_q(X^9)_rR^{55}$ (wherein X^9 is as defined hereinbefore, q is 0 or 1, r is 0 or 1, and R^{54} and R^{55} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the proviso that R^{54} cannot be hydrogen);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in R^5X^1- which is linked to X^1 may bear one or more substituents selected from hydroxy, halogeno and amino); R^1 represents hydrogen, oxo, halogeno, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkoxymethyl, C_{1-4}alkanoyl, C_{1-4}haloalkyl, cyano, amino, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-3}alkanoyloxy, nitro, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, N-C_{1-4}alkylcarbamoyl, N,N-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di(C_{1-4}alkyl)aminosulphonyl, N-(C_{1-4}alkylsulphonyl)amino, N-(C_{1-4}alkylsulphonyl)-N-(C_{1-4}alkyl)amino, N,N-di(C_{1-4}alkylsulphonyl)amino, a C_{3-7}alkylene chain joined to two ring C carbon atoms, C_{1-4}alkanoylaminoC_{1-4}alkyl, carboxy or a group $R^{56}X^{10}$ (wherein X^{10} represents a direct bond, -O-, -CH_2-, -OC(O)-, -C(O)-, -S-, -SO-, -SO_2-, -NR^{57}C(O)-, -C(O)NR^{58}-, -SO_2NR^{59}-, -$NR^{60}SO_2$- or -NR^{61}- (wherein R^{57}, R^{58}, R^{59}, R^{60} and R^{61} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^{56} is selected from one of the following twenty-two groups:

1) hydrogen, oxiranylC_{1-4}alkyl or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) C_{1-5}alkylX^{11}C(O)R^{62} (wherein X^{11} represents -O- or -NR^{63}- (in which R^{63} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{62} represents C_{1-3}alkyl, -$NR^{64}R^{65}$ or -OR^{66} (wherein R^{64}, R^{65} and R^{66} which may be the same or different each represents hydrogen, C_{1-5}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkyl$X^{12}R^{67}$ (wherein X^{12} represents -O-, -S-, -SO-, -SO_2-, -OC(O)-, -NR^{68}C(O)-, -C(O)NR^{69}-, -SO_2NR^{70}-, -$NR^{71}SO_2$- or -NR^{72}- (wherein R^{68}, R^{69}, R^{70}, R^{71} and R^{72} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{67} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected

independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

4) C_{1-5}alkyl$X^{13}C_{1-5}$alkyl$X^{14}R^{73}$ (wherein X^{13} and X^{14} which may be the same or different are each -O-, -S-, -SO-, $-SO_2-$, $-NR^{74}C(O)-$, $-C(O)NR^{75}-$, $-SO_2NR^{76}-$, $-NR^{77}SO_2-$ or $-NR^{78}-$ (wherein R^{74}, R^{75}, R^{76}, R^{77} and R^{78} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{73} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

5) R^{79} (wherein R^{79} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

6) C_{1-5}alkylR^{79} (wherein R^{79} is as defined hereinbefore);

7) C_{2-5}alkenylR^{79} (wherein R^{79} is as defined hereinbefore);

8) C_{2-5}alkynylR^{79} (wherein R^{79} is as defined hereinbefore);

9) R^{80} (wherein R^{80} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from oxo, hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $-C(O)NR^{81}R^{82}$, $-NR^{83}C(O)R^{84}$ (wherein R^{81}, R^{82}, R^{83} and R^{84}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

10) C_{1-5}alkylR^{80} (wherein R^{80} is as defined hereinbefore);

11) C_{2-5}alkenylR^{80} (wherein R^{80} is as defined hereinbefore);

12) C_{2-5}alkynylR^{80} (wherein R^{80} is as defined hereinbefore);

13) C_{1-5}alkyl$X^{15}R^{80}$ (wherein X^{15} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{85}C(O)-$, $-C(O)NR^{86}-$, $-SO_2NR^{87}-$, $-NR^{88}SO_2-$ or $-NR^{89}-$ (wherein R^{85}, R^{86}, R^{87}, R^{88} and R^{89} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined hereinbefore);

14) C_{2-5}alkenyl$X^{16}R^{80}$ (wherein X^{16} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{90}C(O)-$, $-C(O)NR^{91}-$, $-SO_2NR^{92}-$, $-NR^{93}SO_2-$ or $-NR^{94}-$ (wherein R^{90}, R^{91}, R^{92}, R^{93} and R^{94} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined hereinbefore);

15) C_{2-5}alkynyl$X^{17}R^{80}$ (wherein X^{17} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{95}C(O)-$, $-C(O)NR^{96}-$, $-SO_2NR^{97}-$, $-NR^{98}SO_2-$ or $-NR^{99}-$ (wherein R^{95}, R^{96}, R^{97}, R^{98} and R^{99} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined hereinbefore);

16) C_{1-4}alkyl$X^{18}C_{1-4}$alkylR^{80} (wherein X^{18} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{100}C(O)-$, $-C(O)NR^{101}-$, $-SO_2NR^{102}-$, $-NR^{103}SO_2-$ or $-NR^{104}-$ (wherein R^{100}, R^{101}, R^{102}, R^{103} and R^{104} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined hereinbefore);

17) C_{1-4}alkyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore);

21) C_{2-5}alkynyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined hereinbefore); and

22) C_{1-4}alkyl$R^{105}(C_{1-4}$alkyl$)_x(X^{18})_yR^{106}$ (wherein X^{18} is as defined hereinbefore, x is 0 or 1, y is 0 or 1, and R^{105} and R^{106} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O,

S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl) with the proviso that R^{105} cannot be hydrogen);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in $R^{56}X^{10}$- which is linked to X^{10} may bear one or more substituents selected from hydroxy, halogeno and amino);

with the proviso that one or more R^1 and/or one or more R^2 are selected from one of the following three groups:

(i) Q^1X^1-

wherein X^1 is as defined hereinbefore and Q^1 is selected from one of the following nine groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, C_{1-6}fluoroalkanoyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, C_{1-6}fluoroalkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

2) C_{1-5}alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, -SO_2-, -OC(O)-, -NQ^3C(O)-, -C(O)NQ^4-, -SO_2NQ^5-, -NQ^6SO_2- or –NQ^7- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore;

3) C_{1-5}alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) C_{2-5}alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

5) C_{2-5}alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, -SO_2-, -NQ^8C(O)-, -C(O)NQ^9-, -SO_2NQ^{10}-, -$NQ^{11}SO_2$- or –NQ^{12}- (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each

independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore);

7) C_{2-5}alkenylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

8) C_{2-5}alkynylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore); and

9) C_{1-4}alkyl$Q^{13}(C_{1-4}alkyl)_j(W^2)_kQ^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, C_{1-6}fluoroalkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the provisos that Q^{13} cannot be hydrogen and one or both of Q^{13} and Q^{14} must be a 5-6-membered saturated or partially unsaturated heterocyclic group as defined hereinbefore which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, C_{1-6}fluoroalkanoyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group optionally bears 1 or 2 further substituents selected from those defined hereinbefore); and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in Q^1X^1- which is linked to X^1 may bear one or more substituents selected from hydroxy, halogeno and amino);

(ii) $Q^{15}W^3$-

wherein W^3 represents –$NQ^{16}C(O)$-, -$C(O)NQ^{17}$-, -SO_2NQ^{18}-, -$NQ^{19}SO_2$- or –NQ^{20}- (wherein Q^{16}, Q^{17}, Q^{18}, Q^{19} and Q^{20} each independently represents C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}haloalkyl), and Q^{15} is C_{1-6}haloalkyl, C_{2-5}alkenyl or C_{2-5}alkynyl; and

(iii) $Q^{21}W^4C_{1-5}$alkylX^1- wherein W^4 represents –$NQ^{22}C(O)$-, -$C(O)NQ^{23}$-, -SO_2NQ^{24}-, -$NQ^{25}SO_2$- or –NQ^{26}- (wherein Q^{22}, Q^{23}, Q^{24}, Q^{25} and Q^{26} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl), and Q^{21} represents C_{1-6}haloalkyl, C_{2-5}alkenyl or C_{2-5}alkynyl, and X^1 is as defined hereinbefore;

or a salt thereof, or a prodrug thereof for example an ester or an amide, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

According to one aspect of the present invention ring C is a 9-10-membered aromatic bicyclic moiety which may optionally contain 1-3 heteroatoms selected independently from O, N and S.

According to one aspect of the present invention ring C is a 9-10-membered heteroaromatic bicyclic moiety which contains 1-3 heteroatoms selected independently from O, N and S.

According to one aspect of the present invention ring C is a 9-10-membered heteroaromatic bicyclic moiety which contains 1 or 2 nitrogen atoms.

According to one aspect of the present invention ring C is indolyl, quinolinyl, indazolyl or azaindolyl.

According to one aspect of the present invention ring C is indolyl, indazolyl or azaindolyl.

According to one aspect of the present invention ring C is indolyl or azaindolyl.

According to one aspect of the present invention ring C is azaindolyl.

According to one aspect of the present invention ring C is indolyl.

According to one aspect of the present invention ring C is indazolyl.

According to one aspect of the present invention ring Z is -O- or -S-.

According to one aspect of the present invention ring Z is -O-.

In one embodiment of the present invention X^1 represents a direct bond, -O-, -S-, -$NR^6C(O)$-, -NR^9SO_2- or -NR^{10}- (wherein R^6, R^9 and R^{10} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

In one embodiment of the present invention X^1 represents a direct bond, -O-, -S-, -$NR^6C(O)$-, -NR^9SO_2- (wherein R^6 and R^9 each independently represents hydrogen or C_{1-2}alkyl) or NH.

In one embodiment of the present invention X^1 represents -O-, -S-, -$NR^6C(O)$- (wherein R^6 represents hydrogen or C_{1-2}alkyl) or NH.

In one embodiment of the present invention X^1 represents -O- or -$NR^6C(O)$- (wherein R^6 represents hydrogen or C_{1-2}alkyl).

In one embodiment of the present invention X^1 represents -O- or -NHC(O)-.

In one embodiment of the present invention X^1 represents -O-.

According to another aspect of the present invention X^1 represents -O- or a direct bond.

In one embodiment of the present invention R^1 is selected from one of the three groups:

(i) Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore;

and/or R^1 represents oxo, hydroxy, C_{1-2}alkoxymethyl, amino, halogeno, C_{1-2}alkyl, C_{1-2}alkoxy, trifluoromethyl, cyano, nitro, C_{2-3}alkanoyl.

According to one aspect of the present invention R^1 represents methyl, ethyl, trifluoromethyl or halogeno.

According to another aspect of the present invention R^1 represents methyl, fluoro, chloro or bromo.

According to another aspect of the present invention R^1 represents methyl or fluoro.

In one embodiment of the present invention n is 3.

In one embodiment of the present invention n is 2.

In one embodiment of the present invention n is 1.

In one embodiment of the present invention n is 0.

In one embodiment of the present invention n is 0, 1 or 2.

In one embodiment of the present invention m is 1 or 2.

In one embodiment of the present invention m is 1.

In one embodiment of the present invention m is 2.

In one embodiment of the present invention X^3 represents -O-, -S-, -SO-, $-SO_2$-, $-SO_2NR^{19}$- or $-NR^{21}$- (wherein R^{19} and R^{21} each independently represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

In one embodiment of the present invention X^3 represents -O- or $-NR^{21}$- (wherein R^{21} represents hydrogen or C_{1-2}alkyl).

In one embodiment of the present invention X^3 represents -O-.

In one embodiment of the present invention X^4 and X^5 which may be the same or different each represents -O-, -S- or $-NR^{27}$- (wherein R^{27} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

In one embodiment of the present invention X^4 and X^5 which may be the same or different each represents -O- or -NH-.

In one embodiment of the present invention X^4 and X^5 each represents -O-.

In one embodiment of the present invention X^6 represents -O-, -S- or -NR^{38}- (wherein R^{38} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

In one embodiment of the present invention X^6 represents -O- or -NR^{38}- (wherein R^{38} represents hydrogen or C_{1-2}alkyl).

In one embodiment of the present invention X^6 represents -O-.

In one embodiment of the present invention X^7 represents -O-, -S- or -NR^{43}- (wherein R^{43} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

In one embodiment of the present invention X^7 represents -O- or -NR^{43}- (wherein R^{43} represents hydrogen or C_{1-2}alkyl).

In one embodiment of the present invention X^7 represents -O-.

In one embodiment of the present invention X^8 represents -O-, -S- or -NR^{48}- (wherein R^{48} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

In one embodiment of the present invention X^8 represents -O- or -NR^{48}- (wherein R^{48} represents hydrogen or C_{1-2}alkyl).

In one embodiment of the present invention X^8 represents -O-.

In one embodiment of the present invention X^9 represents -O-, -S- or -NR^{53}- (wherein R^{53} represents hydrogen, C_{1-2}alkyl or C_{1-2}alkoxyethyl).

In one embodiment of the present invention X^9 represents -O- or -NR^{53}- (wherein R^{53} represents hydrogen or C_{1-2}alkyl).

In one embodiment of the present invention X^9 represents -O-.

In one embodiment of the present invention R^{28} is pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, 1,3-dioxolan-2-yl, morpholino or thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl, C_{1-3}alkylamino, di(C_{1-3}alkyl)amino, C_{1-3}alkylaminoC_{1-3}alkyl, di(C_{1-3}alkyl)aminoC_{1-3}alkyl, C_{1-3}alkylaminoC_{1-3}alkoxy, di(C_{1-3}alkyl)aminoC_{1-3}alkoxy and a group -(-O-)$_f$(C_{1-3}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

In one embodiment of the present invention R^{28} is pyrrolidinyl, piperazinyl, piperidinyl, 1,3-dioxolan-2-yl, morpholino or thiomorpholino which group may bear 1 or 2

substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl and C_{1-2}alkylsulphonylC_{1-3}alkyl.

In one embodiment of the present invention R^{29} is phenyl, pyridyl, imidazolyl, thiazolyl or triazolyl group which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}alkoxy, cyano and $-NR^{32}C(O)R^{33}$ (wherein R^{32} and R^{33} are each independently selected from hydrogen and C_{1-4}alkyl).

In one embodiment of the present invention R^{54} and R^{55} are each selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, morpholino and thiomorpholino which group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-3}cyanoalkyl, C_{1-3}alkyl, C_{1-3}hydroxyalkyl, C_{1-3}alkoxy, C_{1-2}alkoxyC_{1-3}alkyl, C_{1-2}alkylsulphonylC_{1-3}alkyl, C_{1-3}alkoxycarbonyl and a group $-(-O-)_f(C_{1-3}alkyl)_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a heterocyclic group selected from pyrrolidinyl, piperazinyl, piperidinyl, imidazolidinyl, morpholino and thiomorpholino, which cyclic group may bear one or more substituents selected from C_{1-3}alkyl).

In one embodiment of the present invention R^2 is selected from one of the three groups:

(i) Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore;

and/or R^2 represents hydroxy, C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is as hereinbefore defined and R^5 represents methyl, ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 2-(ethylamino)ethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-diethylamino)ethyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 2-(methylpiperidino)ethyl, 2-(ethylpiperidino)ethyl, 2-((2-methoxyethyl)piperidino)ethyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, (1-(2-

methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(piperazin-1-yl)ethyl, (pyrrolidin-2-yl)methyl, (2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, 5(*R*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (5*S*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphinyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2*R*)-3-piperidino-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl or (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl].

In one embodiment of the present invention R^2 is selected from one of the three groups:

(i) Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore;

and/or R^2 represents hydroxy, C_{1-3}alkyl, amino or R^5X^1- [wherein X^1 is -O- and R^5 represents methyl, ethyl, benzyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(methylsulphinyl)ethyl, 2-(methylsulphonyl)ethyl, 2-(ethylsulphinyl)ethyl, 2-(ethylsulphonyl)ethyl, 2-(N,N-dimethylsulphamoyl)ethyl, 2-(N-methylsulphamoyl)ethyl, 2-sulphamoylethyl, 2-(methylamino)ethyl, 2-(ethylamino)ethyl, 2-(N,N-dimethylamino)ethyl, 2-(N,N-diethylamino)ethyl, 2-(N-methyl-N-methylsulphonylamino)ethyl, 3-(N-methyl-N-methylsulphonylamino)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 2-(methylpiperidino)ethyl, 2-(ethylpiperidino)ethyl, 2-((2-methoxyethyl)piperidino)ethyl, 2-((2-methylsulphonyl)ethylpiperidino)ethyl, 3-((2-methylsulphonyl)ethylpiperidino)propyl, (1-cyanomethylpiperidin-3-yl)methyl, (1-cyanomethylpiperidin-4-yl)methyl, 2-(1-cyanomethylpiperidin-3-yl)ethyl, 2-(1-cyanomethylpiperidin-4-yl)ethyl, 3-(1-cyanomethylpiperidin-3-yl)propyl, 3-(1-cyanomethylpiperidin-4-yl)propyl, ((2-methoxyethyl)piperidin-3-yl)methyl, ((2-methoxyethyl)piperidin-4-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-3-yl)methyl, (1-(2-methylsulphonylethyl)piperidin-4-yl)methyl, 2-((2-methylsulphonylethyl)piperidin-3-yl)ethyl, 2-((2-methylsulphonylethyl)piperidin-4-yl)ethyl, 3-((2-methylsulphonylethyl)piperidin-3-yl)propyl, 3-((2-methylsulphonylethyl)piperidin-4-yl)propyl, 2-(piperidin-4-yloxy)ethyl, 3-(piperidin-4-yloxy)propyl, 2-(1-(cyanomethyl)piperidin-4-yloxy)ethyl, 3-(1-(cyanomethyl)piperidin-4-yloxy)propyl, 2-(1-(2-cyanoethyl)piperidin-4-yloxy)ethyl, 3-(1-(2-cyanoethyl)piperidin-4-yloxy)propyl, 2-(piperazin-1-yl)ethyl, (pyrrolidin-2-yl)methyl, (2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, 5(*R*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (5*S*)-(2-oxo-tetrahydro-2*H*-pyrrolidin-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, 2-(1,3-dioxolan-2-yl)ethyl, 2-(2-methoxyethylamino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl, 2-(2-hydroxyethylamino)ethyl, 3-(2-methoxyethylamino)propyl, 3-(N-(2-methoxyethyl)-N-methylamino)propyl, 3-(2-hydroxyethylamino)propyl, 2-methylthiazol-4-ylmethyl, 2-acetamidothiazol-4-ylmethyl, 1-methylimidazol-2-ylmethyl, 2-(imidazol-1-yl)ethyl, 2-(2-methylimidazol-1-yl)ethyl, 2-(2-ethylimidazol-1-yl)ethyl, 3-(2-methylimidazol-1-yl)propyl, 3-

(2-ethylimidazol-1-yl)propyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,3-triazol-2-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 2-(1,2,4-triazol-4-yl)ethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 3-(4-pyridyl)propyl, 2-(4-pyridyloxy)ethyl, 2-(4-pyridylamino)ethyl, 2-(4-oxo-1,4-dihydro-1-pyridyl)ethyl, 2-(2-oxo-imidazolidin-1-yl)ethyl, 3-(2-oxo-imidazolidin-1-yl)propyl, 2-thiomorpholinoethyl, 3-thiomorpholinopropyl, 2-(1,1-dioxothiomorpholino)ethyl, 3-(1,1-dioxothiomorpholino)propyl, 2-(2-methoxyethoxy)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 3-(methylsulphinyl)propyl, 3-(methylsulphonyl)propyl, 3-(ethylsulphinyl)propyl, 3-(ethylsulphonyl)propyl, 2-(5-methyl-1,2,4-triazol-1-yl)ethyl, morpholino, 2-((N-(1-methylimidazol-4-ylsulphonyl)-N-methyl)amino)ethyl, 2-((N-(3-morpholinopropylsulphonyl)-N-methyl)amino)ethyl, 3-(4-oxidomorpholino)propyl, 2-(2-(4-methylpiperazin-1-yl)ethoxy)ethyl, 3-(2-(4-methylpiperazin-1-yl)ethoxy)propyl, 2-(2-morpholinoethoxy)ethyl, 3-(2-morpholinoethoxy)propyl, 2-(tetrahydropyran-4-yloxy)ethyl, 3-(tetrahydropyran-4-yloxy)propyl, 2-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)vinyl, 3-((2-(pyrrolidin-1-yl)ethyl)carbamoyl)prop-2-en-1-yl, 1-(2-morpholinoethyl)piperidin-4-ylmethyl, 1-(2-thiomorpholinoethyl)piperidin-4-ylmethyl, 3-morpholino-2-hydroxypropyl, (2*R*)-3-morpholino-2-hydroxypropyl, (2*S*)-3-morpholino-2-hydroxypropyl, 3-piperidino-2-hydroxypropyl, (2*R*)-3-piperidino-2-hydroxypropyl, (2*S*)-3-piperidino-2-hydroxypropyl, 3-(1-methylpiperazin-4-yl)-2-hydroxypropyl, (2*R*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl or (2*S*)-3-(1-methylpiperazin-4-yl)-2-hydroxypropyl].

In one embodiment of the present invention R^2 substituents are at the 6- and/or 7-positions of the quinazoline ring.

In one embodiment of the present invention R^2 is selected from one of the three groups:

(i) Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore;

and/or R^2 represents methoxy.

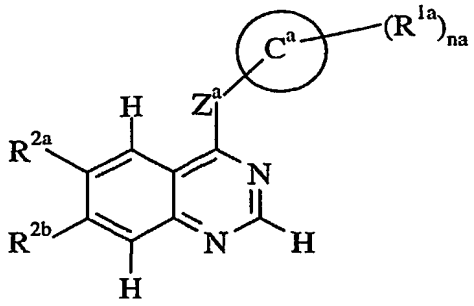
In one embodiment of the present invention R^2 is Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore and/or R^2 represents methoxy.

In one embodiment of the present invention R^2 is $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore and/or R^2 represents methoxy.

In one embodiment of the present invention R^2 is $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore and/or R^2 represents methoxy.

According to another aspect of the present invention there are provided compounds of the formula I.

According to another aspect of the present invention there are provided compounds of the formula II:



(II)

[wherein:

ring C^a is indolyl, indazolyl or azaindolyl;

R^{1a} is selected from oxo, hydroxy, C_{1-2}alkoxymethyl, amino, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, cyano, nitro, C_{1-3}alkanoyl,

(i) Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore;

R^{2a} and R^{2b}, are each independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl, $-NR^{3a}R^{4a}$ (wherein R^{3a} and R^{4a}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl),

(i) Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore;

Z^a is -O- or -S-;

and na is 0, 1 or 2;

with the proviso that at least one of R^{2a} and R^{2b} is selected from (i), (ii) and (iii) as defined hereinbefore and/or R^{1a} is selected from (i), (ii) and (iii) as defined hereinbefore;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

According to another aspect of the present invention there are provided compounds of the formula II as defined hereinbefore wherein at least one of R^{2a} and R^{2b} is selected from (i), (ii) and (iii) as defined hereinbefore.

In one embodiment of the present invention Z^a is -O-.

In one embodiment of the present invention C^a is indol-5-yl, indol-6-yl, 7-azaindol-5-yl, indazol-5-yl, indazol-6-yl.

In one embodiment of the present invention R^{1a} is halogeno or C_{1-3}alkyl.

In one embodiment of the present invention R^{1a} is fluoro or methyl.

In one embodiment of the present invention R^{2a} is methoxy and R^{2b} is selected from one of the three following groups:

(i) Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore.

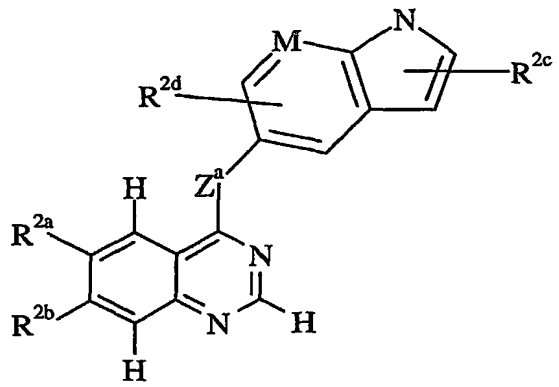
In another embodiment of the present invention R^{2b} is methoxy and R^{2a} is selected from one of the three following groups:

(i) Q^1X^1 wherein Q^1 and X^1 are as defined hereinbefore;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined hereinbefore; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined hereinbefore.

According to another aspect of the present invention there are provided compounds of the formula IIa:



(IIa)

[wherein:

M is -CH- or -N-;

R^{2c} is linked to a carbon atom of the 5-membered ring and is selected from hydrogen and methyl;

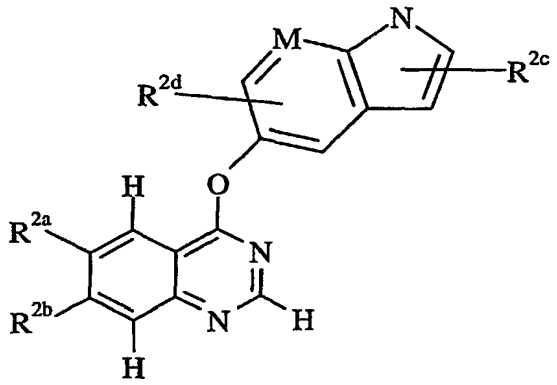
R^{2d} is linked to a carbon atom of the 6-membered ring and is selected from hydrogen and fluoro;

Z^a, R^{2a} and R^{2b}, are as defined hereinbefore;

with the proviso that at least one of R^{2a} and R^{2b} is selected from (i), (ii) and (iii) as defined hereinbefore;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

According to another aspect of the present invention there are provided compounds of the formula IIb:



(IIb)

[wherein:

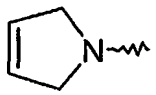
M is -CH- or -N-;

R^{2c} is linked to a carbon atom of the 5-membered ring and is selected from hydrogen and methyl;

R^{2d} is linked to a carbon atom of the 6-membered ring and is selected from hydrogen and fluoro;

one of R^{2a} and R^{2b} is methoxy and the other is Q^1X^1 wherein X^1 is as defined hereinbefore and Q^1 is selected from one of the following nine groups:

1) Q^2 (wherein Q^2 is a heterocyclic group selected from pyrrolidinyl, piperidinyl, piperazinyl,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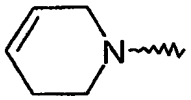
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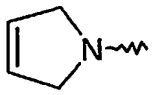
which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}fluoroalkyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl and C_{1-4}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}fluoroalkyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is selected from from pyrrolidinyl, piperidinyl, piperazinyl,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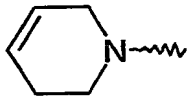
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which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl));

2) C_{1-5}alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, $-SO_2$-, -OC(O)-, $-NQ^3C(O)$-, $-C(O)NQ^4$-, $-SO_2NQ^5$-, $-NQ^6SO_2$- or $-NQ^7$- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, C_{1-2}alkyl, C_{1-2}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore;

3) C_{1-5}alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) C_{2-5}alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

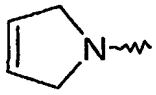
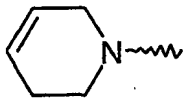
5) C_{2-5}alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, $-SO_2$-, $-NQ^8C(O)$-, $-C(O)NQ^9$-, $-SO_2NQ^{10}$-, $-NQ^{11}SO_2$- or $-NQ^{12}$- (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore);

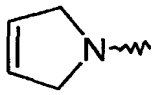
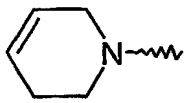
7) C_{2-5}alkenylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

8) C_{2-5}alkynylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore); and

9) C_{1-4}alkyl$Q^{13}(C_{1-4}$alkyl$)_j(W^2)_kQ^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from pyrrolidinyl, piperidinyl, piperazinyl,


and

,

which heterocyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}fluoroalkyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is selected from pyrrolidinyl, piperidinyl, piperazinyl,


and

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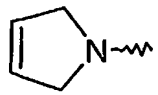
which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the proviso that at least one of Q^{13} and Q^{14} bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}fluoroalkyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl and C_{1-4}fluoroalkylsulphonyl);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in Q^1X^1- which is linked to X^1 may bear one or more substituents selected from hydroxy, halogeno and amino); and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

In one embodiment of the present invention one of R^{2a} and R^{2b} is methoxy and the other is Q^1X^1 wherein X^1 is -O- and Q^1 is selected from one of the following four groups:

1) Q^2 (wherein Q^2 is a heterocyclic group selected from pyrrolidinyl, piperidinyl, piperazinyl,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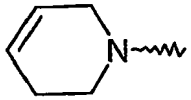
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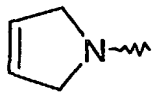
which heterocyclic group bears one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}fluoroalkyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl and C_{1-4}fluoroalkylsulphonyl;

2) C_{1-5}alkylQ^2 (wherein Q^2 is as defined hereinbefore);

3) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

4) C_{1-4}alkyl$Q^{13}(C_{1-4}$alkyl$)_j(W^2)_kQ^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from pyrrolidinyl, piperidinyl, piperazinyl,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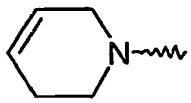
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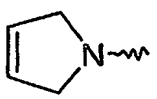
which heterocyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}fluoroalkyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl;

with the proviso that at least one of Q^{13} and Q^{14} bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}fluoroalkyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl and C_{1-4}fluoroalkylsulphonyl);

and additionally wherein any C_{1-5}alkyl, group in Q^1X^1- which is linked to X^1 may bear one or more substituents selected from hydroxy, halogeno and amino).

In one embodiment of the present invention one of R^{2a} and R^{2b} is methoxy and the other is Q^1X^1 wherein X^1 is -O- and Q^1 is selected from one of the following four groups:

1) Q^2 (wherein Q^2 is a heterocyclic group selected from pyrrolidinyl, piperidinyl, piperazinyl,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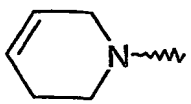
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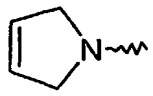
which heterocyclic group bears one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl and C_{1-4}fluoroalkylsulphonyl;

2) C_{1-5}alkylQ^2 (wherein Q^2 is as defined hereinbefore);

3) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

4) C_{1-4}alkyl$Q^{13}(C_{1-4}alkyl)_j(W^2)_kQ^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from pyrrolidinyl, piperidinyl, piperazinyl,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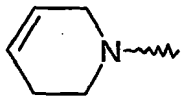
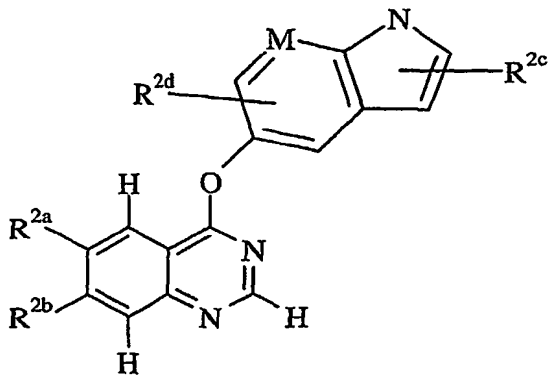

,

which heterocyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl;

with the proviso that at least one of Q^{13} and Q^{14} bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}alkanoyl, C_{1-4}fluoroalkanoyl, C_{1-4}alkylsulphonyl and C_{1-4}fluoroalkylsulphonyl);

and additionally wherein any C_{1-5}alkyl, group in Q^1X^1- which is linked to X^1 may bear one or more substituents selected from hydroxy, halogeno and amino).

According to another aspect of the present invention there are provided compounds of the formula IIc:



(IIc)

[wherein:

M is -CH- or -N-;

R^{2c} is linked to a carbon atom of the 5-membered ring and is selected from hydrogen and methyl;

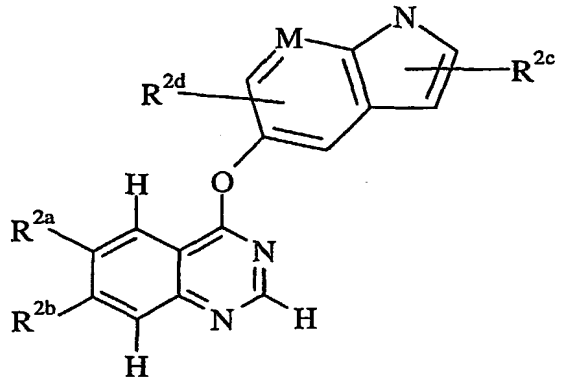
R^{2d} is linked to a carbon atom of the 6-membered ring and is selected from hydrogen and fluoro;

R^{2a} and R^{2b} are each independently selected from methoxy, $Q^{15}W^3$ (wherein Q^{15} and W^3 are as defined hereinbefore) and $Q^{21}W^4C_{1-5}alkylX^1$- (wherein Q^{21}, W^4 and X^1 are as defined hereinbefore);

with the proviso that R^{2a} and R^{2b} cannot both be methoxy;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

According to another aspect of the present invention there are provided compounds of the formula IId:



(IId)

[wherein:

M is -CH- or -N-;

R^{2c} is linked to a carbon atom of the 5-membered ring and is selected from hydrogen and methyl;

R^{2d} is linked to a carbon atom of the 6-membered ring and is selected from hydrogen and fluoro;

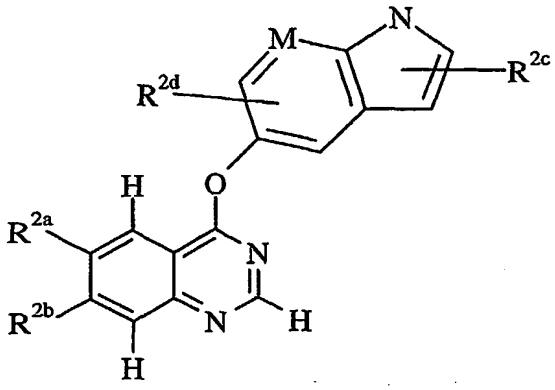
R^{2a} and R^{2b} are each independently selected from methoxy, $Q^{15}W^3$ (wherein W^3 represents $-NQ^{16}C(O)$-, $-C(O)NQ^{17}$-, $-SO_2NQ^{18}$-, $-NQ^{19}SO_2$- or $-NQ^{20}$- (wherein Q^{16}, Q^{17}, Q^{18}, Q^{19} and Q^{20} each independently represents C_{2-5}alkenyl or C_{2-5}alkynyl), and Q^{15} is C_{2-5}alkenyl or C_{2-5}alkynyl), and

$Q^{21}W^4C_{1-5}alkylX^1$- (wherein W^4 represents $-NQ^{22}C(O)$-, $-C(O)NQ^{23}$-, $-SO_2NQ^{24}$-, $-NQ^{25}SO_2$- or $-NQ^{26}$- (wherein Q^{22}, Q^{23}, Q^{24}, Q^{25} and Q^{26} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl), and Q^{21} represents C_{2-5}alkenyl or C_{2-5}alkynyl, and X^1 is as defined hereinbefore);

with the proviso that R^{2a} and R^{2b} cannot both be methoxy;

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

According to another aspect of the present invention there are provided compounds of the formula IIe:



(IIe)

[wherein:

M is -CH- or -N-;

R^{2c} is linked to a carbon atom of the 5-membered ring and is selected from hydrogen and methyl;

R^{2d} is linked to a carbon atom of the 6-membered ring and is selected from hydrogen and fluoro;

one of R^{2a} and R^{2b} is methoxy and the other is selected from Q^1X^1- (wherein X^1 is -O- and Q^1 is C_{1-5}alkylQ^2 (wherein Q^2 is a heterocyclic group selected from pyrrolidinyl, piperidinyl and piperazinyl, which heterocyclic group bears one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}fluoroalkyl, C_{1-4}alkanoyl and C_{1-4}alkylsulphonyl)) and $Q^{21}W^4C_{1-5}alkylX^1$- (wherein X^1 is -O-, W^4 is NQ^{26} (wherein Q^{26} is hydrogen or C_{1-3}alkyl) and Q^{21} is C_{2-5}alkynyl);

and salts thereof, and prodrugs thereof for example esters, amides and sulphides, preferably esters and amides.

In one embodiment of the present invention R^{2a} is methoxy.

In one embodiment of the present invention R^{2b} is selected from Q^1X^1- (wherein X^1 is -O- and Q^1 is C_{1-5}alkylQ^2 (wherein Q^2 is a heterocyclic group selected from pyrrolidinyl, piperidinyl and piperazinyl, which heterocyclic group bears one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}alkanoyl and C_{1-4}alkylsulphonyl)) and $Q^{21}W^4C_{1-5}$alkylX^1- (wherein X^1 is -O-, W^4 is NQ^{26} (wherein Q^{26} is hydrogen or C_{1-3}alkyl) and Q^{21} is C_{2-5}alkenyl).

Compounds of the present invention include

6-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-7-methoxyquinazoline,

4-(7-azaindol-5-yloxy)-7-methoxy-6-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline,

6-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(7-azaindol-5-yloxy)-7-methoxyquinazoline,

4-(7-azaindol-5-yloxy)-6-methoxy-7-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline,

4-(7-azaindol-5-yloxy)-6-methoxy-7-[2-(*N*-methyl-*N*-prop-2-yn-1-ylamino)ethoxy]quinazoline,

4-(4-fluoro-2-methylindol-5-yloxy)-7-methoxy-6-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline,

4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline, and

6-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(4-fluoroindol-5-yloxy)-7-methoxyquinazoline

and salts thereof.

Compounds of the present invention include

7-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(7-azaindol-5-yloxy)-6-methoxyquinazoline, and

7-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline

and salts thereof.

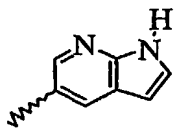
Another compound of the present invention is 4-(7-azaindol-5-yloxy)-7-(3-(4-(2-fluoroethyl)piperazin-1-yl)propoxy)-6-methoxyquinazoline

and salts thereof.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

In this specification unless stated otherwise the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a C_{6-10} aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, alkoxy, nitro, trifluoromethyl and cyano, (wherein alkyl and alkoxy are as hereinbefore defined). The term "aryloxy" as used herein unless otherwise stated includes "aryl"-O-groups in which "aryl" is as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in which "alkyl" and "aryl" are as hereinbefore defined. The term "alkanoyl" as used herein unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example C_2alkanoyl is ethanoyl and refers to $CH_3C{=}O$, C_1alkanoyl is formyl and refers to CHO. Butanoyl refers to CH_3-CH_2-CH_2-C(O), isobutyryl refers to $(CH_3)_2$.CH-C(O). In this specification unless stated otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms. Unless stated otherwise the term "haloalkyl" refers to an alkyl group as defined hereinbefore which bears one or more halogeno groups, such as for example trifluoromethyl.

In this specification the term azaindolyl refers to the moiety (1*H*-pyrrolo[2,3-*b*]pyridinyl) and an analogous convention applies to similar groups. For example 7-azaindol-5-yl is (1*H*-pyrrolo[2,3-*b*]pyridin-5-yl) and is the group:



Within the present invention it is to be understood that a compound of the formula I or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits VEGF receptor tyrosine kinase activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated that compounds of the formula I or a salt thereof may possess an asymmetric carbon atom. Such an asymmetric carbon atom is also involved in the tautomerism described above, and it is to be understood that the present invention encompasses any chiral form (including both pure enantiomers, scalemic and racemic mixtures) as well as any tautomeric form which inhibits VEGF receptor tyrosine kinase activity, and is not to be limited merely to any one tautomeric form or chiral form utilised within the formulae drawings. It is to be understood that the invention encompasses all optical and diastereomers which inhibit VEGF receptor tyrosine kinase activity. It is further to be understood that in the names of chiral compounds (*R*,*S*) denotes any scalemic or racemic mixture while (*R*) and (*S*) denote the enantiomers. In the absence of (*R*,*S*), (*R*) or (*S*) in the name it is to be understood that the name refers to any scalemic or racemic mixture, wherein a scalemic mixture contains *R* and *S* enantiomers in any relative proportions and a racemic mixture contains *R* and *S* enantiomers in the ration 50:50.

It is also to be understood that certain compounds of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit VEGF receptor tyrosine kinase activity.

For the avoidance of any doubt, it is to be understood that when X^1 is, for example, a group of formula $-NR^6C(O)-$, it is the nitrogen atom bearing the R^6 group which is attached to the quinazoline ring and the carbonyl (C(O)) group is attached to R^5, whereas when X^1 is, for example, a group of formula $-C(O)NR^7-$, it is the carbonyl group which is attached to the quinazoline ring and the nitrogen atom bearing the R^7 group is attached to R^5. A similar convention applies to the other two atom X^1 linking groups such as $-NR^9SO_2-$ and $-SO_2NR^8-$.

When X^1 is $-NR^{10}-$ it is the nitrogen atom bearing the R^{10} group which is linked to the quinazoline ring and to R^5. An analogous convention applies to other groups. It is further to be understood that when X^1 represents $-NR^{10}-$ and R^{10} is $C_{1-3}alkoxyC_{2-3}alkyl$ it is the $C_{2-3}alkyl$ moiety which is linked to the nitrogen atom of X^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when R^5 is, for example, a group of formula $C_{1-3}alkylX^9C_{1-3}alkylR^{29}$, it is the terminal $C_{1-3}alkyl$ moiety which is linked to X^1, similarly when R^5 is, for example, a group of formula $C_{2-5}alkenylR^{28}$ it is the $C_{2-5}alkenyl$ moiety which is linked to X^1 and an analogous convention applies to other groups. When R^5 is a group $1\text{-}R^{29}prop\text{-}1\text{-}en\text{-}3\text{-}yl$ it is the first carbon to which the group R^{29} is attached and it is the third carbon which is linked to X^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when R^5 is, for example, R^{28} and R^{28} is a pyrrolidinyl ring which bears a group $-(-O-)_f(C_{1-4}alkyl)_gringD$, it is the -O- or $C_{1-4}alkyl$ which is linked to the pyrrolidinyl ring, unless f and g are both 0 when it is ring D which is linked to the pyrrolidinyl ring and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^{29} carries a $C_{1-4}aminoalkyl$ substituent it is the $C_{1-4}alkyl$ moiety which is attached to R^{29} whereas when R^{29} carries a $C_{1-4}alkylamino$ substituent it is the amino moiety which is attached to R^{29} and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^{28} carries a $C_{1-4}alkoxyC_{1-4}alkyl$ substituent it is the $C_{1-4}alkyl$ moiety which is attached to R^{28} and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when Q^1 is a group $C_{1-5}alkylW^1Q^2$ it is the $C_{1-5}alkyl$ group which is linked to X^1 which is in turn linked to the quinazoline ring. Similarly when Q^1 is a group $C_{2-5}alkenylQ^2$ it is the $C_{2-5}alkenyl$ group which is linked to X^1 which is in turn linked to the quinazoline ring. An analogous convention applies to similar groups.

For the avoidance of any doubt, it is to be understood that when R^2 is a group $Q^{15}W^3$ it is the W^3 group which is linked to the quinazoline ring.

For the avoidance of any doubt, it is to be understood that when R^2 is a group $Q^{21}W^4C_{1-5}alkylX^1$ it is the X^1 group which is linked to the quinazoline ring.

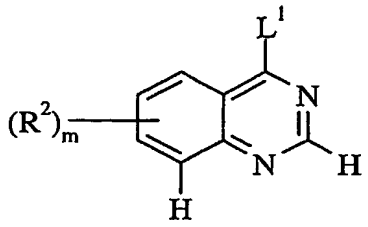
The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A compound of the formula I, or salt thereof, and other compounds of the invention (as herein defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in International Patent Application Number WO 00/47212 and in European Patent Applications Publication Nos. 0520722, 0566226, 0602851 and 0635498. Such processes also include, for example, solid phase synthesis. Such processes, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus, the following processes (a) to (f) and (i) to (vi) constitute further features of the present invention.

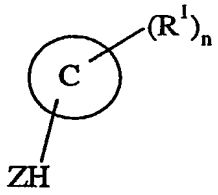
Synthesis of Compounds of Formula I

(a) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula III:



(III)

(wherein R^2 and m are as defined hereinbefore and L^1 is a displaceable moiety), with a compound of the formula IV:



(IV)

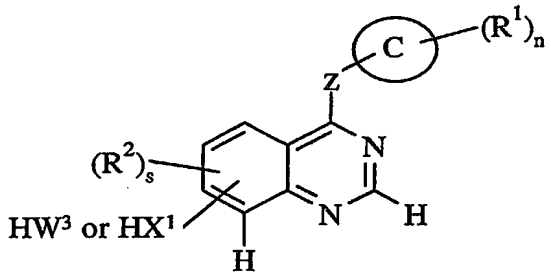
(wherein ring C, R^1, Z and n are as defined hereinbefore) to obtain compounds of the formula I and salts thereof. A convenient displaceable moiety L^1 is, for example, a halogeno, alkoxy (preferably C_{1-4}alkoxy), aryloxy, alkylsulphanyl, arylsulphanyl, alkoxyalkylsulphanyl or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methylsulphanyl, 2-methoxyethylsulphanyl, methanesulphonyloxy or toluene-4-sulphonyloxy group.

The reaction is advantageously effected in the presence of a base. Such a base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, cesium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, or an alkali metal or alkaline earth metal amide, for example sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The reaction is preferably effected in the presence of an inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene,

or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethyl sulphoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 90°C.

When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide, for example hydrogen chloride, sulphuric acid, a sulphonic acid, for example methane sulphonic acid, or a carboxylic acid, for example acetic or citric acid, using a conventional procedure.

(b) Production of those compounds of formula I and salts thereof wherein at least one R^2 is R^5X^1, Q^1X^1, $Q^{15}W^3$ or $Q^{21}W^4C_{1-5}alkylX^1$, wherein R^5, Q^1, Q^{15}, W^3, Q^{21} and W^4 are as defined hereinbefore, and X^1 is -O-, -S-, -OC(O)- or $-NR^{10}-$ (wherein R^{10} independently represents hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl) can be achieved by the reaction, conveniently in the presence of a base (as defined hereinbefore in process (a)) of a compound of the formula V:



(V)

(wherein ring C, Z, W^3, R^1, R^2 and n are as hereinbefore defined and X^1 is as hereinbefore defined in this section and s is an integer from 0 to 2) with one of the compounds of the formulae VIa-d:

R^5-L^1 (VIa)

Q^1-L^1 (VIb)

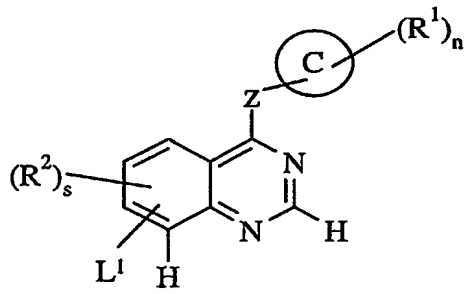
Q^{15}-L^1 (VIc)

Q^{21}-W^4-C_{1-5}alkyl-L^1 (VId)

(wherein R^5, Q^1, Q^{15}, Q^{21} and W^4 and L^1 are as hereinbefore defined), L^1 is a displaceable moiety for example a halogeno or sulphonyloxy group such as a bromo, methanesulphonyloxy

or toluene-4-sulphonyloxy group, or L^1 may be generated in situ from an alcohol under standard Mitsunobu conditions ("Organic Reactions", John Wiley & Sons Inc, 1992, vol 42, chapter 2, David L Hughes). The reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 50°C.

(c) Compounds of the formula I and salts thereof wherein at least one R^2 is R^5X^1, Q^1X^1, $Q^{15}W^3$ or $Q^{21}W^4C_{1-5}alkylX^1$, wherein R^5, Q^1, Q^{15}, W^3, Q^{21} and W^4 are as defined hereinbefore, and X^1 is -O-, -S-, -OC(O)- or $-NR^{10}-$ (wherein R^{10} represents hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl) may be prepared by the reaction of a compound of the formula VII:



(VII)

with one of the compounds of the formulae VIIIa-d:

R^5-X^1-H (VIIIa)

Q^1-X^1-H (VIIIb)

Q^{15}-W^3-H (VIIIc)

Q^{21}-W^4-C_{1-5}alkyl-X^1-H (VIIId)

(wherein L^1, R^1, R^2, R^5, Q^1, Q^{15}, W^3, Q^{21}, W^4, ring C, Z, n and s are all as hereinbefore defined and X^1 is as hereinbefore defined in this section). The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

(d) Compounds of the formula I and salts thereof wherein at least one R^2 is R^5X^1, Q^1X^1 or $Q^{21}W^4C_{1-5}alkylX^1$, wherein X^1 is as defined hereinbefore, R^5 is $C_{1-5}alkylR^{113}$, wherein R^{113} is selected from one of the following nine groups:

1) $X^{19}C_{1-3}alkyl$ (wherein X^{19} represents -O-, -S-, $-SO_2-$, $-NR^{114}C(O)-$ or $-NR^{115}SO_2-$ (wherein R^{114} and R^{115} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$);

2) $NR^{116}R^{117}$ (wherein R^{116} and R^{117} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$);

3) $X^{20}C_{1-5}alkylX^5R^{22}$ (wherein X^{20} represents -O-, -S-, $-SO_2-$, $-NR^{118}C(O)-$, $-NR^{119}SO_2-$ or $-NR^{120}-$ (wherein R^{118}, R^{119}, and R^{120} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and X^5 and R^{22} are as defined hereinbefore);

4) R^{28} (wherein R^{28} is as defined hereinbefore);

5) $X^{21}R^{29}$ (wherein X^{21} represents -O-, -S-, $-SO_2-$, $-NR^{121}C(O)-$, $-NR^{122}SO_2-$, or $-NR^{123}-$ (wherein R^{121}, R^{122}, and R^{123} which may be the same or different are each hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{29} is as defined hereinbefore); and

6) $X^{22}C_{1-3}alkylR^{29}$ (wherein X^{22} represents -O-, -S-, $-SO_2-$, $-NR^{124}C(O)-$, $-NR^{125}SO_2-$ or $-NR^{126}-$ (wherein R^{124}, R^{125} and R^{126} each independently represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{29} is as defined hereinbefore);

7) R^{29} (wherein R^{29} is as defined hereinbefore);

8) $X^{22}C_{1-4}alkylR^{28}$ (wherein X^{22} and R^{28} are as defined hereinbefore); and

9) $R^{54}(C_{1-4}alkyl)_q(X^9)_rR^{55}$ (wherein q, r, X^9, R^{54} and R^{55} are as defined hereinbefore);

Q^1 is $C_{1-5}alkylQ^{27}$ wherein Q^{27} is selected from:

10) W^1Q^2 (wherein W^1 and Q^2 are as defined hereinbefore);

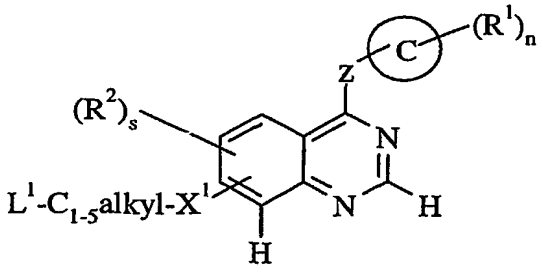
11) Q^2 (wherein Q^2 is as defined hereinbefore);

12) $W^2C_{1-4}alkylQ^2$ (wherein W^2 and Q^2 are as defined hereinbefore); and

13) $Q^{13}(C_{1-4}alkyl)_j(W^2)_kQ^{14}$ (wherein W^2, j, k, Q^{13} and Q^{14} are as defined hereinbefore); and

Q^{21} and W^4 are as defined hereinbefore,

may be prepared by reacting a compound of the formula IX:



(IX)

(wherein L^1, X^1, R^1, R^2, ring C, Z, n and s are as hereinbefore defined) with one of the compounds of the formulae Xa-c:

R^{113}-H (Xa)

Q^{27}-H (Xb)

Q^{21}-W^4-H (Xc)

(wherein R^{113}, Q^{27}, Q^{21} and W^4 are as defined hereinbefore) to give a compound of the formula I or salt thereof. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), and at a temperature in the range, for example 0 to 150°C, conveniently at about 50°C.

Processes (a), (b) and (d) are preferred over process (c).

Processes (a) and (b) are the more preferred.

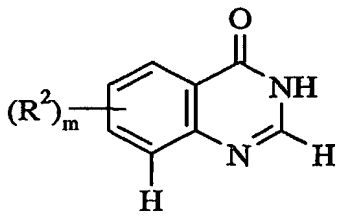
(e) The production of those compounds of the formula I and salts thereof wherein one or more of the substituents $(R^2)_m$ is represented by -$NR^{127}R^{128}$, where one (and the other is hydrogen) or both of R^{127} and R^{128} are C_{1-3}alkyl, may be effected by the reaction of compounds of formula I wherein the substituent $(R^2)_m$ is an amino group and an alkylating agent, preferably in the presence of a base as defined hereinbefore. Such alkylating agents are C_{1-3}alkyl moieties bearing a displaceable moiety as defined hereinbefore such as C_{1-3}alkyl halides for example C_{1-3}alkyl chloride, bromide or iodide. The reaction is preferably effected in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)) and at a temperature in the range, for example, 10 to 100°C, conveniently at about ambient temperature. The production of compounds of formula I and salts thereof wherein one or

more of the substituents R^2 is an amino group may be effected by the reduction of a corresponding compound of formula I wherein the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s). The reduction may conveniently be effected as described in process (i) hereinafter. The production of a compound of formula I and salts thereof wherein the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s) may be effected by the processes described hereinbefore and hereinafter in processes (a-d) and (i-v) using a compound selected from the compounds of the formulae (I-XXII) in which the substituent(s) at the corresponding position(s) of the quinazoline group is/are a nitro group(s).

(f) Compounds of the formula I and salts thereof wherein X^1 is -SO- or $-SO_2-$ may be prepared by oxidation from the corresponding compound in which X^1 is -S- or -SO- (when X^1 is $-SO_2-$ is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

Synthesis of Intermediates

(i) The compounds of formula III and salts thereof in which L^1 is halogeno may for example be prepared by halogenating a compound of the formula XI:

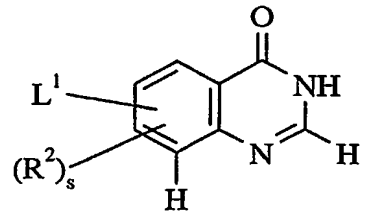


(XI)

wherein R^2 and m are as hereinbefore defined).

Convenient halogenating agents include inorganic acid halides, for example thionyl chloride, phosphorus(III)chloride, phosphorus(V)oxychloride and phosphorus(V)chloride. The halogenation reaction may be effected in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, or an aromatic hydrocarbon solvent such as benzene or toluene, or the reaction may be effected without the presence of a solvent. The reaction is conveniently effected at a temperature in the range, for example 10 to 150°C, preferably in the range 40 to 100°C.

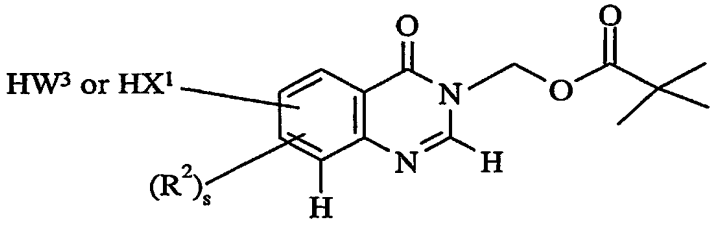
The compounds of formula XI and salts thereof may, for example, be prepared by reacting a compound of the formula XII:



(XII)

(wherein R^2, s and L^1 are as hereinbefore defined) with one of the compounds of formulae VIIIa-d as hereinbefore defined. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

Compounds of formula XI and salts thereof wherein at least one R^2 is R^5X^1, Q^1X^1, $Q^{15}W^3$ or $Q^{21}W^4C_{1-5}alkylX^1$, wherein R^5, Q^1, Q^{15}, W^3, Q^{21} and W^4 are as defined hereinbefore, and wherein X^1 is -O-, -S-, -SO-, $-SO_2-$, -C(O)-, $-C(O)NR^7-$, $-SO_2NR^8-$ or $-NR^{10}-$ (wherein R^7, R^8 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl), may for example also be prepared by the reaction of a compound of the formula XIII:

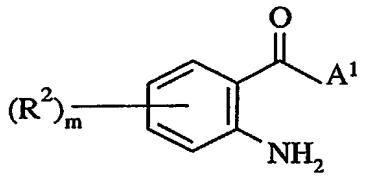


(XIII)

(wherein R^2, W^3 and s are as hereinbefore defined and X^1 is as hereinbefore defined in this section) with one of the compounds of formulae VIa-d as hereinbefore defined. The reaction may for example be effected as described for process (b) hereinbefore. The pivaloyloxymethyl group can then be cleaved by reacting the product with a base such as, for example, aqueous ammonia, triethylamine in water, an alkali metal or alkaline earth metal hydroxide or alkoxide, preferably aqueous ammonia, aqueous sodium hydroxide or aqueous

potassium hydroxide, in a polar protic solvent such as an alcohol, for example methanol or ethanol. The reaction is conveniently effected at a temperature in the range 20 to 100°C, preferably in the range 20 to 50°C.

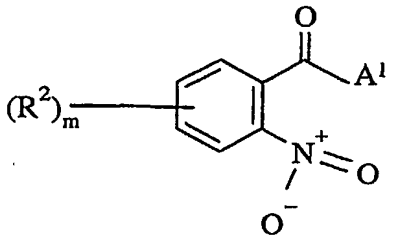
The compounds of formula XI and salts thereof may also be prepared by cyclising a compound of the formula XIV:



(XIV)

(wherein R^2 and m, are as hereinbefore defined, and A^1 is an hydroxy, alkoxy (preferably C_{1-4}alkoxy) or amino group) whereby to form a compound of formula XI or salt thereof. The cyclisation may be effected by reacting a compound of the formula XIV, where A^1 is an hydroxy or alkoxy group, with formamide or an equivalent thereof effective to cause cyclisation whereby a compound of formula XI or salt thereof is obtained, such as [3-(dimethylamino)-2-azaprop-2-enylidene]dimethylammonium chloride. The cyclisation is conveniently effected in the presence of formamide as solvent or in the presence of an inert solvent or diluent such as an ether for example 1,4-dioxan. The cyclisation is conveniently effected at an elevated temperature, preferably in the range 80 to 200°C. The compounds of formula XI may also be prepared by cyclising a compound of the formula XIV, where A^1 is an amino group, with formic acid or an equivalent thereof effective to cause cyclisation whereby a compound of formula XI or salt thereof is obtained. Equivalents of formic acid effective to cause cyclisation include for example a tri-C_{1-4}alkoxymethane, for example triethoxymethane and trimethoxymethane. The cyclisation is conveniently effected in the presence of a catalytic amount of an anhydrous acid, such as a sulphonic acid for example p-toluenesulphonic acid, and in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as diethyl ether or tetrahydrofuran, or an aromatic hydrocarbon solvent such as toluene. The cyclisation is conveniently effected at a temperature in the range, for example 10 to 100°C, preferably in the range 20 to 50°C.

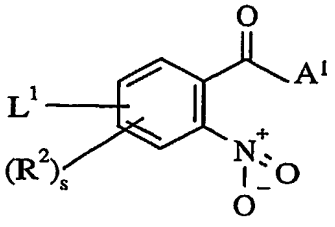
Compounds of formula XIV and salts thereof may for example be prepared by the reduction of the nitro group in a compound of the formula XV:



(XV)

(wherein R^2, m and A^1 are as hereinbefore defined) to yield a compound of formula XIV as hereinbefore defined. The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation. The reduction may be carried out, for example, by stirring a solution of the nitro compound under hydrogen at 1 to 4 atmospheres pressure in the presence of an inert solvent or diluent as defined hereinbefore in the presence of a metal effective to catalyse hydrogenation reactions such as palladium or platinum. A further reducing agent is, for example, an activated metal such as activated iron (produced for example by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be effected by heating the nitro compound under hydrogen at 2 atmospheres pressure in the presence of the activated metal and a solvent or diluent such as a mixture of water and alcohol, for example methanol or ethanol, at a temperature in the range, for example 50 to 150°C, conveniently at about 70°C.

Compounds of the formula XV and salts thereof may for example be prepared by the reaction of a compound of the formula XVI:

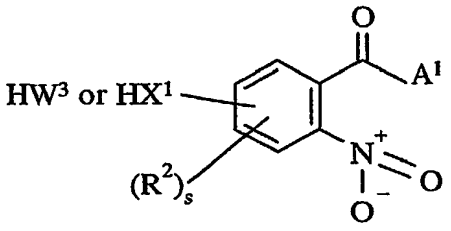


(XVI)

(wherein R^2, s, L^1 and A^1 are as hereinbefore defined) with one of the compounds of formulae VIIIa-d as hereinbefore defined to give a compound of the formula XV. The reaction of the

compounds of formulae XVI and VIIIa-d is conveniently effected under conditions as described for process (c) hereinbefore.

Compounds of formula XV and salts thereof wherein at least one R^2 is R^5X^1, Q^1X^1, $Q^{15}W^3$ or $Q^{21}W^4C_{1-5}alkylX^1$, wherein R^5, Q^1, Q^{15}, W^3, Q^{21} and W^4 are as defined hereinbefore, and wherein X^1 is -O-, -S-, $-SO_2-$, -C(O)-, $-C(O)NR^7-$, $-SO_2NR^8-$ or $-NR^{10}-$ (wherein R^7, R^8 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl), may for example also be prepared by the reaction of a compound of the formula XVII:



(XVII)

(wherein R^2, s and A^1 are as hereinbefore defined and X^1 is as hereinbefore defined in this section) with one of the compounds of formulae VIa-d as hereinbefore defined to yield a compound of formula XV as hereinbefore defined. The reaction of the compounds of formulae XVII and VIa-d is conveniently effected under conditions as described for process (b) hereinbefore.

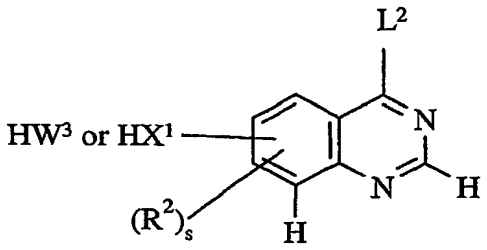
The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is $-CH_2-$ may be prepared for example as described above from a compound of the formula XV (in which R^2 is $-CH_3$) or XIII (in which HX^1- is $-CH_3$), by radical bromination or chlorination to give a $-CH_2Br$ or $-CH_2Cl$ group which may then be reacted with a compound of the formula R^5-H under standard conditions for such substitution reactions.

The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is a direct bond may be prepared for example as described above from a compound of the formula XI, wherein the R^5 group is already present in the intermediate compounds (for example in a compound of the formula XV) used to prepare the compound of formula XI.

The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1 and wherein X^1 is $-NR^6C(O)-$ or $-NR^9SO_2-$ may be prepared for example from a compound of the formula XIII in which HX^1- is an $-NHR^6-$ or $-NHR^9-$ group (prepared for example from an

amino group (later functionalised if necessary) by reduction of a nitro group) which is reacted with an acid chloride or sulfonyl chloride compound of the formula R^5COCl or R^5SO_2Cl.

The compounds of formula III and salts thereof wherein at least one R^2 is R^5X^1, Q^1X^1, $Q^{15}W^3$ or $Q^{21}W^4C_{1-5}alkylX^1$, wherein R^5, Q^1, Q^{15}, W^3, Q^{21} and W^4 are as defined hereinbefore, and wherein X^1 is -O-, -S-, $-SO_2-$, -OC(O)-, $-C(O)NR^7-$, $-SO_2NR^8-$ or $-NR^{10}-$ (wherein R^7, R^8 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or $C_{1-3}alkoxyC_{2-3}$alkyl), may also be prepared for example by reacting a compound of the formula XVIII:

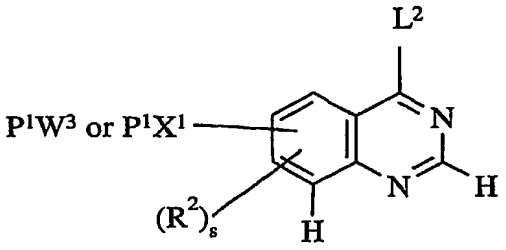


(XVIII)

(wherein R^2, W^3 and s are as hereinbefore defined, X^1 is as hereinbefore defined in this section and L^2 represents a displaceable protecting moiety) with one of the compounds of formulae VIa-d as hereinbefore defined, whereby to obtain a compound of formula III in which L^1 is represented by L^2.

A compound of formula XVIII is conveniently used in which L^2 represents a phenoxy group which may if desired carry up to 5 substituents, preferably up to 2 substituents, selected from halogeno, nitro and cyano. The reaction may be conveniently effected under conditions as described for process (b) hereinbefore.

The compounds of formula XVIII and salts thereof may for example be prepared by deprotecting a compound of the formula XIX:



(XIX)

(wherein R^2, W^3, s and L^2 are as hereinbefore defined, P^1 is a protecting group and X^1 is as hereinbefore defined in the section describing compounds of the formula XVIII). The choice of protecting group P^1 is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in Organic Synthesis" T.W. Greene and R.G.M.Wuts, 2nd Ed. Wiley 1991, including N-sulphonyl derivatives (for example, p-toluenesulphonyl), carbamates (for example, t-butyl carbonyl), N-alkyl derivatives (for example, 2-chloroethyl, benzyl) and amino acetal derivatives (for example benzyloxymethyl). The removal of such a protecting group may be effected by any of the procedures known for such a transformation, including those reaction conditions indicated in standard texts such as that indicated hereinbefore, or by a related procedure. Deprotection may be effected by techniques well known in the literature, for example where P^1 represents a benzyl group deprotection may be effected by hydrogenolysis or by treatment with trifluoroacetic acid.

One compound of formula III may if desired be converted into another compound of formula III in which the moiety L^1 is different. Thus for example a compound of formula III in which L^1 is other than halogeno, for example optionally substituted phenoxy, may be converted to a compound of formula III in which L^1 is halogeno by hydrolysis of a compound of formula III (in which L^1 is other than halogeno) to yield a compound of formula XI as hereinbefore defined, followed by introduction of halide to the compound of formula XI, thus obtained as hereinbefore defined, to yield a compound of formula III in which L^1 represents halogen.

(ii) Compounds of formula IV and salts thereof in which ring C is indolyl may be prepared by any of the methods known in the art, such as for example those described in "Indoles Part I", "Indoles Part II", 1972 John Wiley & Sons Ltd and "Indoles Part III" 1979, John Wiley & Sons Ltd, edited by W. J. Houlihan.

Examples of the preparation of indoles are given in Examples 1 and 10 hereinafter.

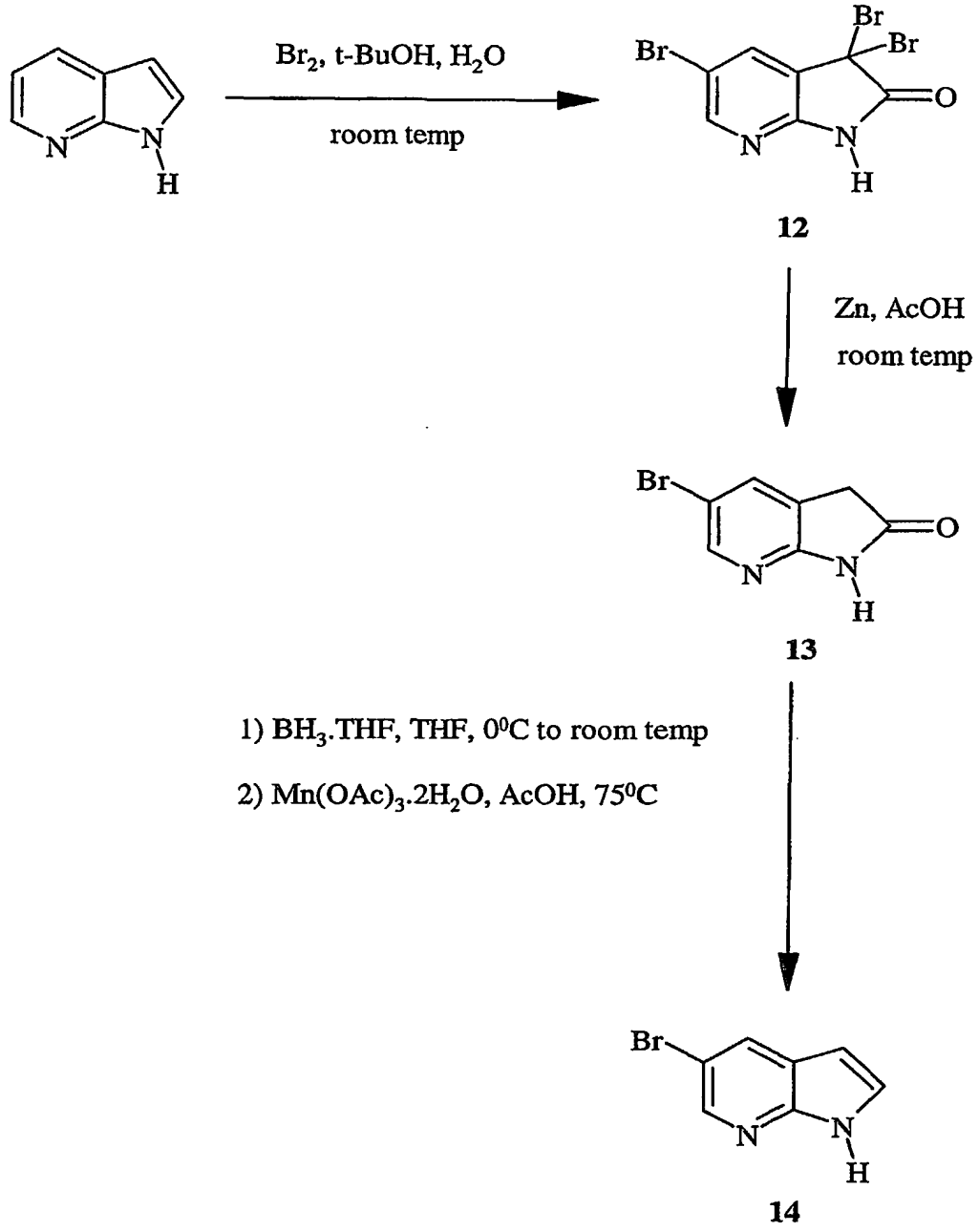
Compounds of formula IV and salts thereof in which ring C is quinolinyl may be prepared by any of the methods known in the art, such as for example those described in "The Chemistry of Heterocyclic Compounds: Quinolines Parts I, II and III", 1982 (Interscience publications) John Wiley & Sons Ltd, edited by G. Jones, and in "Comprehensive Heterocyclic Chemistry Vol II by A. R. Katritzky", 1984 Pergamon Press, edited by A. J. Boulton and A McKillop.

Compounds of formula IV and salts thereof in which ring C is indazolyl may be prepared by any of the methods known in the art, such as for example those described in Petitcoles, Bull. Soc. Chim. Fr. 1950, 466 and Davies, J. Chem. Soc. 1955, 2412.

Compounds of formula IV and salts thereof in which ring C is azaindolyl may be prepared by any of the methods known in the art, such as for example those described in Heterocycles 50, (2), 1065-1080, 1999. They may also be made according to the process in Example 2 hereinafter.

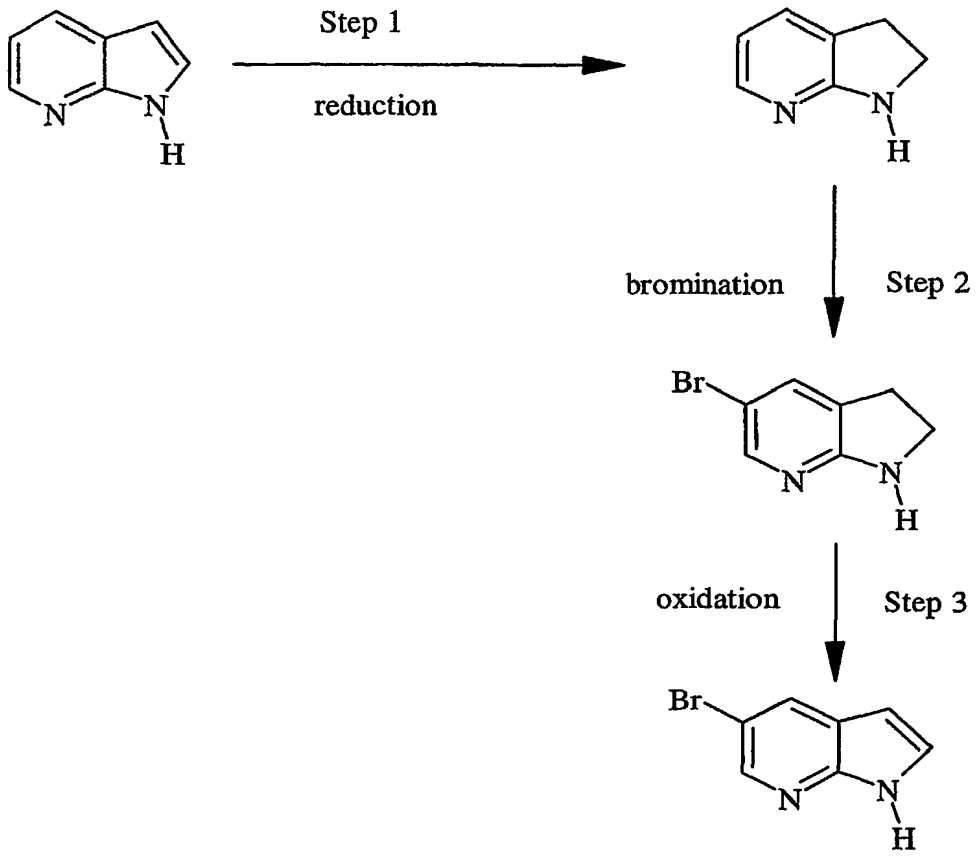
In Heterocycles 50, (2), 1065-1080, 1999 a process is described, shown in Scheme 1 hereinafter, wherein 7-azaindole is halogenated to give 3,3,5-tribromo-2-oxo-1,3-dihydropyrrolo[2,3-*b*]pyridine (**12**). **12** is then treated with zinc in acetic acid to give 5-bromo-2-oxo-1,3-dihydropyrrolo[2,3-*b*]pyridine (**13**) and **13** is then treated via two steps to give 5-bromo-7-azaindole (**14**). This synthesis is shown in Scheme 1:

Scheme 1



Surprisingly we have found that it is better to synthesise the 5-bromo-7-azaindole by three steps outlined in Scheme 2:

Scheme 2



Scheme 2 is surprisingly better than Scheme 1. Scheme 2 requires smaller quantities of reagent and is more adaptable for large scale manufacture because it is cheaper, more efficient and more enviromentally friendly than Scheme 1.

Step 1:

The reduction may be carried out by any of the procedures known for such a transformation. The reduction may be carried out, for example, by treating a solution of 7-azaindole in an alcohol, for example ethanol, or another solvent for example decahydronaphthalene, with wet Raney Nickel and then stirring the mixture in a hydrogen atmosphere under pressure, for example at 5 atmospheres pressure, at 50 to 150^{0}C, preferably at about 95^{0}C, over a period of time, for example 2 days, to give, after purification, 7-azaindoline.

Step 2:

The bromination may be carried out by any of the procedures known for such a reaction. The bromination may be carried out, for example, by mixing 7-azaindoline, p-

toluene sulphonic acid monohydrate and 1,3-dibromo-5,5-dimethylhydantoin in methylene chloride and stirring the mixture at for example ambient temperature for a period of time, for example 3 hours. Extraction and purification gives 5-bromo-7-azaindoline.

Step 3:

The oxidation may be carried out by any of the procedures known for such a transformation. The oxidation may be carried out, for example, by mixing 5-bromo-7-azaindoline and precipitated, active manganese (IV) oxide in toluene, then heating the mixture at 50 to 150^{0}C, preferably at about 90^{0}C to give 5-bromo-7-azaindole.

In Heterocycles 50, (2), 1065-1080, 1999 the 5-bromo-7-azaindole (986mg, 5.0mmol) is dissolved, under an inert atmosphere, in a mixture of DMF (32ml) and methanol (20ml). To this solution is added successively sodium methoxide (14.3g, 265mmol) and copper(I)bromide (1.43g, 10.0mmol) at room temperature. The mixture is heated at reflux for 2.5 hours to give, after extraction and purification, 5-methoxy-7-azaindole (530mg, 72%).

We have found that the yield for this reaction is surprisingly and significantly increased from 72% to 97% if the reagents are used in proportionately smaller quantities including for example a different solvent mixture. Thus in Example 2 hereinafter:

"A solution of 5-bromo-7-azaindole (8.6 g, 44 mmol), copper (I) bromide (12.6 g, 88 mmol) and sodium methoxide (100 g, 1.85 mol) in a mixture of "degassed" DMF (260 mls) and methanol (175 mls) was stirred at ambient temperature in a nitrogen atmosphere, and then heated at reflux for 3.5 hours."

After extraction and partial purification this gave crude solid, 5-methoxy-7-azaindole (6.3 g, 97%), which was taken through the next step without further purification.

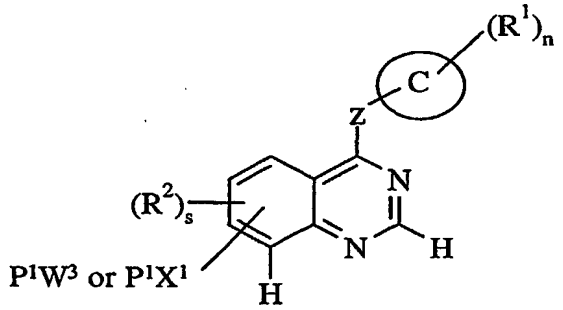
The 5-hydroxy-7-azaindole may be generated from the 5-methoxy-7-azaindole by the following process.

Adding boron tribromide in methylene chloride to a solution of 5-methoxy-7-azaindole in methylene chloride cooled at about –30^{0}C. Leaving the mixture to warm up to ambient temperature and stirring it for a period of time, for example overnight. Pouring the mixture onto ice and water and adjusting the pH of the aqueous phase to about 6. Separating the organic phase and further extracting the aqueous phase with ethyl acetate. Combining the organic phases washing them with brine, drying them, for example over magnesium sulphate, and then evaporating them. The residue may then be purified, for example by column

chromatography eluting with increasingly polar mixtures of methylene chloride and methanol to give 5-hydroxy-7-azaindole.

Alternatively the 5-methoxy-7-azaindole may be suspended in methylene chloride, stirred in a nitrogen atmosphere, cooled in a cold water bath and a 1.0 M solution of boron tribromide in methylene chloride added dropwise over a period of time, for example 30 minutes. The mixture is then allowed to stir at ambient temperature for a period of time, for example 4 hours, before being quenched by taking the solution to about pH7, for example by the dropwise addition of 5N sodium hydroxide. The resulting 2 phase mixture is allowed to separate and the organic phase collected and evaporated *in vacuo*. The residue may be treated with the aqueous phase from above, the mixture adjusted to about pH7 once more and subjected to a continuous ethyl acetate extraction over a period of time for example 18 hours. The resulting ethyl acetate suspension is then evaporated *in vacuo* to give a product which may be purified, for example by column chromatography using Kieselgel 60 silica and methylene chloride/methanol/880 ammonium hydroxide (100/8/1) solvent to give 5-hydroxyazaindole.

(iii) Compounds of formula V as hereinbefore defined and salts thereof may be made by deprotecting the compound of formula XX:



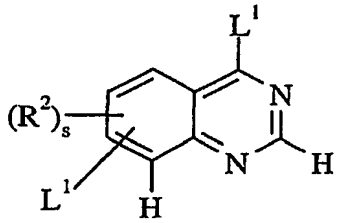
(XX)

(wherein ring C, Z, R^1, R^2, P^1, W^3, n and s are as hereinbefore defined and X^1 is as hereinbefore defined in the section describing compounds of the formula V) by a process for example as described in (i) above.

Compounds of the formula XX and salts thereof may be made by reacting compounds of the formulae XIX and IV as hereinbefore defined, under the conditions described in (a) hereinbefore, to give a compound of the formula XX or salt thereof.

(iv) Compounds of the formula VII and salts thereof may be made by reacting a

compound of the formula XXI:



(XXI)

(wherein R^2, s and each L^1 are as hereinbefore defined and the L^1 in the 4-position and the other L^1 in a further position on the quinazoline ring may be the same or different) with a compound of the formula IV as hereinbefore defined, the reaction for example being effected by a process as described in (a) above.

(v) Compounds of formula IX as defined hereinbefore and salts thereof may for example be made by the reaction of compounds of formula V as defined hereinbefore with compounds of the formula XXII:

$$L^1\text{-}C_{1\text{-}5}\text{alkyl-}L^1 \qquad \text{(XXII)}$$

(wherein L^1 is as hereinbefore defined) to give compounds of formula IX or salts thereof. The reaction may be effected for example by a process as described in (b) above.

(vi) Intermediate compounds wherein X^1 is -SO- or -SO_2- may be prepared by oxidation from the corresponding compound in which X^1 is -S- or -SO- (when X^1 is -SO_2- is required in the final product). Conventional oxidation conditions and reagents for such reactions are well known to the skilled chemist.

When a pharmaceutically acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with, for example, an acid using a conventional procedure, the acid having a pharmaceutically acceptable anion.

Many of the intermediates defined herein are novel and these are provided as a further feature of the invention. The preparation of these compounds is as described herein and/or is by methods well known to persons skilled in the art of organic chemistry.

The identification of compounds which inhibit angiogenesis and/or increased vascular permeability, which potently inhibit the tyrosine kinase activity associated with the

VEGF receptor KDR and are selective for KDR over Flt-1, which have less extended plasma pharmacokinetics and which are inactive or only weakly active in the hERG assay, is desirable and is the subject of the present invention.

These properties may be assessed, for example, using one or more of the procedures set out below:

(a) In Vitro Receptor Tyrosine Kinase Inhibition Test

This assay determines the ability of a test compound to inhibit tyrosine kinase activity. DNA encoding VEGF, FGF or EGF receptor cytoplasmic domains may be obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These may then be expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example VEGF, FGF and EGF receptor cytoplasmic domains, which were obtained by expression of recombinant protein in insect cells, were found to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor Flt-1 (Genbank accession number X51602), a 1.7kb DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 783 and including the termination codon, described by Shibuya et al (Oncogene, 1990, 5: 519-524), was isolated from cDNA and cloned into a baculovirus transplacement vector (for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide, L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)). This recombinant construct was co-transfected into insect cells (for example Spodoptera frugiperda 21(Sf21)) with viral DNA (eg Pharmingen BaculoGold) to prepare recombinant baculovirus. (Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co, New York). For other tyrosine kinases for use in assays, cytoplasmic fragments starting from methionine 806 (KDR, Genbank accession number L04947), methionine 668 (EGF receptor, Genbank accession number X00588) and methionine 399 (FGF R1 receptor, Genbank accession number X51803) may be cloned and expressed in a similar manner.

For expression of cFlt-1 tyrosine kinase activity, Sf21 cells were infected with plaque-pure cFlt-1 recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS)

(10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold HNTG/PMSF (20mM Hepes pH7.5, 150mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM magnesium chloride, 1mM ethylene glycol-bis(βaminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1mM PMSF (phenylmethylsulphonyl fluoride); the PMSF is added just before use from a freshly-prepared 100mM solution in methanol) using 1ml HNTG/PMSF per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C, the supernatant (enzyme stock) was removed and stored in aliquots at -70°C. Each new batch of stock enzyme was titrated in the assay by dilution with enzyme diluent (100mM Hepes pH 7.4, 0.2mM sodium orthovanadate, 0.1% v/v Triton X100, 0.2mM dithiothreitol). For a typical batch, stock enzyme is diluted 1 in 2000 with enzyme diluent and 50µl of dilute enzyme is used for each assay well.

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100µl of diluted substrate solution was dispensed into all wells of assay plates (Nunc maxisorp 96-well immunoplates) which were sealed and left overnight at 4°C.

On the day of the assay the substrate solution was discarded and the assay plate wells were washed once with PBST (PBS containing 0.05% v/v Tween 20) and once with 50mM Hepes pH7.4.

Test compounds were diluted with 10% dimethylsulphoxide (DMSO) and 25µl of diluted compound was transferred to wells in the washed assay plates. "Total" control wells contained 10% DMSO instead of compound. Twenty five microlitres of 40mM manganese(II)chloride containing 8µM adenosine-5'-triphosphate (ATP) was added to all test wells except "blank" control wells which contained manganese(II)chloride without ATP. To start the reactions 50µl of freshly diluted enzyme was added to each well and the plates were incubated at room temperature for 20 minutes. The liquid was then discarded and the wells were washed twice with PBST. One hundred microlitres of mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321), diluted 1 in 6000 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of horse radish peroxidase (HRP)-linked

sheep anti-mouse Ig antibody (Amersham product NXA 931), diluted 1 in 500 with PBST containing 0.5% w/v BSA, was added and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibtion of enzyme activity.

(b) In Vitro HUVEC Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC).

HUVEC cells were isolated in MCDB 131 (Gibco BRL) + 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8), in MCDB 131 + 2% v/v FCS + 3μg/ml heparin + 1μg/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates. After a minimum of 4 hours they were dosed with the appropriate growth factor (i.e. VEGF 3ng/ml, EGF 3ng/ml or b-FGF 0.3ng/ml) and compound. The cultures were then incubated for 4 days at 37°C with 7.5% CO_2. On day 4 the cultures were pulsed with 1μCi/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were harvested using a 96-well plate harvester (Tomtek) and then assayed for incorporation of tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as cpm, was used to measure inhibition of growth factor-stimulated cell proliferation by compounds.

(c) In Vivo Solid Tumour Disease Model

This test measures the capacity of compounds to inhibit solid tumour growth.

CaLu-6 tumour xenografts were established in the flank of female athymic Swiss *nu/nu* mice, by subcutaneous injection of $1x10^6$ CaLu-6 cells/mouse in 100μl of a 50% (v/v) solution of Matrigel in serum free culture medium. Ten days after cellular implant, mice were

allocated to groups of 8-10, so as to achieve comparable group mean volumes. Tumours were measured using vernier calipers and volumes were calculated as: $(l \times w) \times \sqrt{(l \times w)} \times (\pi/6)$, where l is the longest diameter and w the diameter perpendicular to the longest. Test compounds were administered orally once daily for a minimum of 21 days, and control animals received compound diluent. Tumours were measured twice weekly. The level of growth inhibition was calculated by comparison of the mean tumour volume of the control group versus the treatment group using a Student T test and/or a Mann-Whitney Rank Sum Test. The inhibitory effect of compound treatment was considered significant when $p<0.05$.

(d) hERG-encoded Potassium Channel Inhibition Test

This assay determines the ability of a test compound to inhibit the tail current flowing through the human ether-a-go-go-related-gene (hERG)-encoded potassium channel.

Human embryonic kidney (HEK) cells expressing the hERG-encoded channel were grown in Minimum Essential Medium Eagle (EMEM; Sigma-Aldrich catalogue number M2279), supplemented with 10% Foetal Calf Serum (Labtech International; product number 4-101-500), 10% M1 serum-free supplement (Egg Technologies; product number 70916) and 0.4 mg/ml Geneticin G418 (Sigma-Aldrich; catalogue number G7034). One or two days before each experiment, the cells were detached from the tissue culture flasks with Accutase (TCS Biologicals) using standard tissue culture methods. They were then put onto glass coverslips resting in wells of a 12 well plate and covered with 2 ml of the growing media.

For each cell recorded, a glass coverslip containing the cells was placed at the bottom of a Perspex chamber containing bath solution (see below) at room temperature (~20 °C). This chamber was fixed to the stage of an inverted, phase-contrast microscope. Immediately after placing the coverslip in the chamber, bath solution was perfused into the chamber from a gravity-fed reservoir for 2 minutes at a rate of ~ 2 ml/min. After this time, perfusion was stopped.

A patch pipette made from borosilicate glass tubing (GC120F, Harvard Apparatus) using a P-97 micropipette puller (Sutter Instrument Co.) was filled with pipette solution (see hereinafter). The pipette was connected to the headstage of the patch clamp amplifier (Axopatch 200B, Axon Instruments) via a silver/silver chloride wire. The headstage ground was connected to the earth electrode. This consisted of a silver/silver chloride wire embedded in 3% agar made up with 0.85% sodium chloride.

The cell was recorded in the whole cell configuration of the patch clamp technique. Following "break-in", which was done at a holding potential of –80 mV (set by the amplifier), and appropriate adjustment of series resistance and capacitance controls, electrophysiology software (*Clampex*, Axon Instruments) was used to set a holding potential (-80 mV) and to deliver a voltage protocol. This protocol was applied every 15 seconds and consisted of a 1 s step to +40 mV followed by a 1 s step to –50 mV. The current response to each imposed voltage protocol was low pass filtered by the amplifier at 1 kHz. The filtered signal was then acquired, on line, by digitising this analogue signal from the amplifier with an analogue to digital converter. The digitised signal was then captured on a computer running *Clampex* software (Axon Instruments). During the holding potential and the step to + 40 mV the current was sampled at 1 kHz. The sampling rate was then set to 5 kHz for the remainder of the voltage protocol.

The compositions, pH and osmolarity of the bath and pipette solution are tabulated below.

Salt	Pipette (mM)	Bath (mM)
NaCl	-	137
KCl	130	4
$MgCl_2$	1	1
$CaCl_2$	-	1.8
HEPES	10	10
glucose	-	10
Na_2ATP	5	-
EGTA	5	-

Parameter	Pipette	Bath
pH	7.18 – 7.22	7.40
pH adjustment with	1M KOH	1M NaOH
Osmolarity (mOsm)	275-285	285-295

The amplitude of the hERG-encoded potassium channel tail current following the step from +40 mV to –50 mV was recorded on-line by *Clampex* software (Axon Instruments). Following stabilisation of the tail current amplitude, bath solution containing the vehicle for the test substance was applied to the cell. Providing the vehicle application had no significant

effect on tail current amplitude, a cumulative concentration effect curve to the compound was then constructed.

The effect of each concentration of test compound was quantified by expressing the tail current amplitude in the presence of a given concentration of test compound as a percentage of that in the presence of vehicle.

Test compound potency (IC_{50}) was determined by fitting the percentage inhibition values making up the concentration-effect to a four parameter Hill equation using a standard data-fitting package. If the level of inhibition seen at the highest test concentration did not exceed 50%, no potency value was produced and a percentage inhibition value at that concentration was quoted.

Plasma pharmacokinetics may be assessed by measuring plasma half-life in *vivo*. The longer the plasma half-life *in vivo* the more extended are the plasma pharmacokinetics.

Compounds of the present invention have less extended plasma pharmacokinetics than compounds of WO 00/47212. Compounds of the present invention have shorter half-lives *in vivo* than compounds of WO 00/47212.

Plasma half-life *in vivo* may be determined by standard methods which are well-known in the art of plasma pharmacokinetics. Any species may be used and the plasma half-life determined by standard methodology, for example plasma half-life may be measured in rat, dog, monkey or human.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000mg per square metre body area of the animal, i.e.

approximately 0.1-100mg/kg. A unit dose in the range, for example, 1-100mg/kg, preferably 1-50mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250mg of active ingredient.

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit VEGF receptor tyrosine kinase activity and are therefore of interest for their antiangiogenic effects and/or their ability to cause a reduction in vascular permeability.

A further feature of the present invention is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 0.1-50mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of

the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin αvβ3 function, angiostatin, razoxin, thalidomide), and including vascular targeting agents (for example combretastatin phosphate and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchinol-O-phosphate));

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic

agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, and also irinotecan); also enzymes (for example asparaginase); and thymidylate synthase inhibitors (for example raltitrexed);

and additional types of chemotherapeutic agent include:

(iv) biological response modifiers (for example interferon); and

(v) antibodies (for example edrecolomab).

For example such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of a compound of formula I as defined hereinbefore, and a vascular targeting agent described in WO 99/02166 such as N-acetylcolchinol-O-phosphate (Exampe 1 of WO 99/02166).

As stated above the compounds defined in the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, lymphoedema, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Cancer may affect any tissue and includes leukaemia, multiple myeloma and lymphoma. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention are expected to inhibit any form of cancer associated with VEGF including leukaemia, mulitple myeloma and lymphoma and also, for example, the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of VEGF receptor tyrosine kinase activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(viii) HPLC were run under 2 different conditions:

1) on a TSK Gel super ODS 2μM 4.6mm x 5cm column, eluting with a gradient of methanol in water (containing 1% acetic acid) 20 to 100% in 5 minutes. Flow rate 1.4 ml/minute. Detection: U.V. at 254 nm and light scattering detections;

2) on a TSK Gel super ODS 2μM 4.6mm x 5cm column, eluting with a gradient of methanol in water (containing 1% acetic acid) 0 to 100% in 7 minutes. Flow rate 1.4 ml/minute. Detection: U.V. at 254 nm and light scattering detections.

(ix) petroleum ether refers to that fraction boiling between 40-60°C

(x) the following abbreviations have been used:-

DMF N,N-dimethylformamide

DMSO dimethylsulphoxide

TFA trifluoroacetic acid

THF tetrahydrofuran

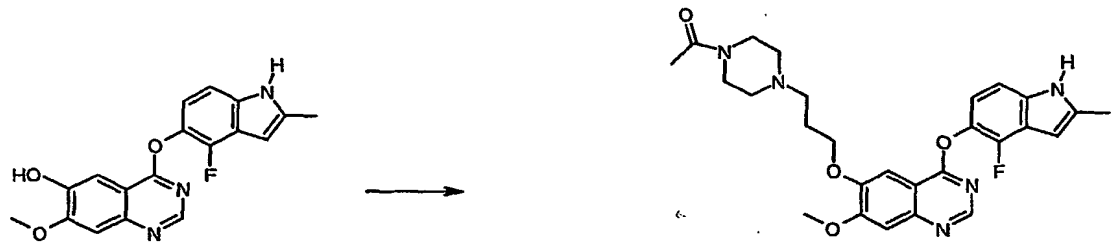
DEAD diethyl azodicarboxylate

DMA dimethylacetamide

DMAP 4-dimethylaminopyridine

LC/MS HPLC coupled to mass spectrometry

Example 1



Diethyl azodicarboxylate (0.178 g, 1.02 mmol) was added to a solution of 4-(4-fluoro-2-methylindol-5-yloxy)-6-hydroxy-7-methoxyquinazoline (0.267g, 0.787 mmol), triphenylphosphine (0.31g, 1.18mmol) and 3-(4-acetylpiperazin-1yl)propan-1-ol (0.176g, 0.945 mmol) in methylene chloride (10 ml). After stirring for 15 minutes at ambient temperature, further triphenylphosphine (0.062mg, 0.236 mmol) and diethyl azodicarboxylate (0.041mg, 0.3mmol) were added. After stirring for 1 hour at ambient temperature, the mixture was poured onto a column of silica and eluted with increasingly polar mixtures of ethyl acetate and methylene chloride followed by methylene chloride and methanol. The fractions containing the expected product were combined and evaporated. The residue was triturated under diethyl ether and the solid was filtered, washed with ether and dried under vacuum to give **6-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-7-methoxyquinazoline** 0.210g, 60%).

NMR spectrum : ($DMSOd_6$, CF_3COOD) 2.1 (s, 3H), 2.35 (m, 2H), 2.45 (s, 3H), 3.0 (m, 2H), 3.2 (m, 1H), 3.4 (dd, 2H), 3.5 (m, 1H), 3.65 (d, 2H), 4.1 (m, 1H), 4.15 (s, 3H), 4.45 (dd, 2H),

4.55 (d, 1H), 6.3 (s, 0.3 H, partly exchanged), 7.05 (dd, 1H), 7.28 (d, 1H), 7.6 (s, 1H), 7.9 (s, 1H), 9.2 (s, 1H)

Mass Spectrum : [M+H]+ 508.5

The starting material was prepared as follows:

A suspension of 1-acetylpiperazine (3.85g, 30 mmol), potassium carbonate (8.3g, 60 mmol) and 3-bromo-1-propanol (4ml, 45 mmol) in acetonitrile (30ml) was heated and stirred at 80^{0}C for 5 hours. After cooling, the mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography, eluting with increasingly polar mixtures of methylene chloride and ethanol. The fractions containing the expected product were combined and evaporated to give 3-(4-acetylpiperazin-1-yl)propan-1-ol (3.15g, 56%).

NMR spectrum ($CDCl_3$) : 1.7 (m, 2H), 2.08 (s, 3H), 2.45 (m, 4H), 2.6 (dd, 2H), 3.45 (dd, 2H), 3.6 (dd, 2H), 3.78 (dd, 2H), 4.6 (br s, 1H)

Mass Spectrum : [M+H]+ 187

A solution of 6-benzyloxy-4-chloro-7-methoxyquinazoline (0.39g, 1.3mmol), (EP1153920 production examples 28-30), 4-fluoro-5-hydroxy-2-methylindole (0.24g, 1.43mmol) and cesium carbonate (1.2g, 4mmol) in DMF (4ml) was stirred at 95^{0}C for 45 minutes. After cooling, the mixture was filtered and the filtrate was evaporated under vacuum. The residue was purified by column chromatography eluting with increasingly polar mixtures of methylene chloride and ethyl acetate to give 6-benzyloxy-4-(4-fluoro-2-methylindol-5-yloxy)-7-methoxyquinazoline (0.213g, 37%).

NMR spectrum (DMSO d_6) 2.42 (s, 3H), 4.05 (s, 3H), 5.3 (s, 2H), 6.25 (s, 1H), 7.0 (dd, 1H), 7.18 (d, 1H), 7.35-7.6 (m, 6H), 7.8 (s, 1H), 8.55 (s, 1H)

Mass spectrum : [M+H]+ 430

A solution of 6-benzyloxy-4-(4-fluoro-2-methylindol-5-yloxy)-7-methoxyquinazoline (1.32g, 3mmol), ammonium formate (1.94g, 30mmol) and 10% palladium on carbon (0.2g) in DMF (15ml) containing water (2ml) was stirred at ambient temperature for 1 hour. The mixture was filtered and the filtrate was evaporated. The residue was triturated under diethyl ether, filtered, washed with diethyl ether followed by water and dried under vacuum over P_2O_5 overnight to give 4-(4-fluoro-2-methylindol-5-yloxy)-6-hydroxy-7-methoxyquinazoline (1g, 100%).

NMR Spectrum ($DMSOd_6$) 2.35 (s, 3H), 4.0 (s, 3H), 6.25 (s, 1H), 7.0 (m, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 8.0 (s, 1H), 8.55 (s, 1H)
Mass spectrum : [M+H]+ 340.

To a solution of 2-fluoro-4-nitroanisole (9.9 g, 58 mmol) and 4-chlorophenoxyacetonitrile (10.7 g, 64 mmol) in DMF (50 ml) cooled at -15°C was added potassium *tert*-butoxide (14.3 g, 127 mmol) in DMF (124 ml). After stirring for 30 minutes at -15°C, the mixture was poured onto cooled 1N hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with 1N sodium hydroxide, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride. The fractions containing the expected product were combined and evaporated. The residue was dissolved in ethanol (180 ml) and acetic acid (24 ml) containing 10 % palladium on charcoal (600 mg) and the mixture was hydrogenated under 3 atmospheres pressure for 2 hours. The mixture was filtered, and the volatiles were removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was separated, and washed with saturated sodium hydrogen carbonate followed by brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with methylene chloride to give a mixture of 4-fluoro-5-methoxyindole and 6-fluoro-5-methoxyindole (5.64 g, 59 %) in a ratio 1/2.

^{1}H NMR Spectrum: ($DMSOd_6$) 3.85 (s, 3H) ; 6.38 (s, 1H, 6-Fluoro) ; 6.45 (s, 1H ; 4-Fluoro) ; 6.9-7.4 (m, 3H)

A solution of 4-fluoro-5-methoxyindole and 6-fluoro-5-methoxyindole in a ratio 1/2 (496 mg, 3 mmol), di-*tert*butyl dicarbonate (720 mg, 3.3 mmol) in acetonitrile (12 ml) containing DMAP (18 mg, 0.15 mmol) was stirred at ambient temperature for 24 hours. The volatiles were removed under vacuum. The residue was dissolved in ethyl acetate, washed with 1N hydrochloric acid, followed by water, brine, dried ($MgSO_4$) and evaporated to give a mixture of 4-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole and 6-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole in a ratio 1/2 (702 mg, 88 %).

^{1}H NMR Spectrum: ($DMSOd_6$) 1.65 (s, 9H) ; 3.9 (s, 3H) ; 6.6 (d, 1H, 6-fluoro) ; 6.72 (d, 1H, 4-fluoro) ; 7.2 (t, 1H, 6-fluoro) ; 7.4 (d, 1H, 4-fluoro) ; 7.62 (d, 1H, 6-fluoro) ; 7.68 (d, 1H, 4-fluoro) ; 7.78 (s, 1H, 4-fluoro) ; 7.85 (s, 1H, 6-fluoro)

To a solution of 4-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole and 6-fluoro-5-methoxy-1-*tert*-butoxycarbonylindole in a ratio 1/2 (8.1 g, 30.5 mmol) in THF (100 ml)

cooled at -65°C was added *tert*-butyllithium (1.7 M) (23 ml, 35.7 mmol). After stirring for 4 hours at -70°C, methyl iodide (8.66 g, 61 mmol) was added and the mixture was left to warm-up to ambient temperature. Water was added and the mixture was extracted with ether. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated and was used directly in the next step.

The crude product was dissolved in methylene chloride (100 ml) and TFA (25 ml) was added. After stirring for 1 hour at ambient temperature, the volatiles were removed under vacuum. The residue was dissolved in ethyl acetate and the organic layer was washed with 1N sodium hydroxide, followed by water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether (3/7) to give 6-fluoro-5-methoxy-2-methylindole (1.6 g) and 4-fluoro-5-methoxy-2-methylindole (0.8 g, 48 %).

6-fluoro-5-methoxy-2-methylindole:

MS-ESI : 180 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 2.35 (s, 3H) ; 3.8 (s, 3H) ; 6.05 (s, 1H) ; 7.1 (s, 1H) ; 7.12 (s, 1H) ; 10.8 (s, 1H)

4-fluoro-5-methoxy-2-methylindole:

MS-ESI : 180 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 2.35 (s, 3H) ; 3.8 (s, 3H) ; 6.15 (s, 1H) ; 6.9 (t, 1H) ; 7.05 (d, 1H) ; 11.0 (s, 1H)

To a solution of 4-fluoro-5-methoxy-2-methylindole (709 mg, 3.95 mmol) in methylene chloride (9 ml) cooled at -30°C was added a solution of boron tribromide (2.18 g, 8.7 mmol) in methylene chloride (1 ml). After stirring for 1 hour at ambient temperature, the mixture was poured onto water and was diluted with methylene chloride. The pH of the aqueous layer was adjusted to 6. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether (3/7) to give 4-fluoro-5-hydroxy-2-methylindole (461 mg, 70 %).

MS-ESI : 166 $[MH]^+$

^1H NMR Spectrum: ($DMSOd_6$) 2.35 (s, 3H) ; 6.05 (s, 1H) ; 6.65 (dd, 1H) ; 6.9 (d, 1H) ; 8.75 (s, 1H) ; 10.9 (s, 1H)

^{13}C NMR Spectrum: ($DMSOd_6$) 13.5 ; 94,0 ; 106,0 ; 112 ; 118.5 (d) ; 132 (d) ; 136 (d) ; 136.5 ; 142.5 (d)

Alternatively the 4-fluoro-5-hydroxy-2-methylindole may be prepared as follows:

To a suspension of sodium hydride (5.42 g, 226 mmol) (prewashed with pentane) in THF (100 ml) cooled at 10°C was added ethyl acetoacetate (29.4 g, 226 mmol) while keeping the temperature below 15°C. After completion of addition, the mixture was further stirred for 15 minutes and cooled to 5°C. A solution of 1,2,3-trifluoro-4-nitrobenzene (20 g, 113 mmol) in THF (150 ml) was added while keeping the temperature below 5°C. The mixture was then left to warm up to ambient temperature and stirred for 24 hours. The volatiles were removed under vacuum and the residue was partitioned between ethyl acetate and 2N aqueous hydrochloric acid. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in concentrated hydrochloric acid (650 ml) and acetic acid (600 ml) and the mixture was refluxed for 15 hours. After cooling, the volatiles were removed under vacuum and the residue was partitioned between aqueous sodium hydrogen carbonate (5 %) and ethyl acetate. The organic layer was washed with sodium hydrogen carbonate, water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethylacetate/petroleum ether (75/25) to give 3-acetylmethyl-1,2-difluoro-4-nitrobenzene (17.5 g, 72 %).

^{1}H NMR Spectrum: ($CDCl_3$) 2.4 (s, 3H) ; 4.25 (s, 2H) ; 7.25 (dd, 1H) ; 8.0 (dd, 1H)

A solution of 3-acetylmethyl-1,2-difluoro-4-nitrobenzene (500 mg, 2.3 mmol) in methylene chloride (5 ml) containing montmorillonite K10 (1 g) and trimethyl orthoformate (5 ml) was stirred for 24 hours at ambient temperature. The solid was filtered, washed with methylene chloride and the filtrate was evaporated to give 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (534 mg, 88 %).

^{1}H NMR Spectrum: ($CDCl_3$) 1.2 (s, 3H) ; 3.2 (s, 6H) ; 3.52 (s, 2H) ; 7.18 (dd, 1H) ; 7.6 (m, 1H)

To a solution of benzyl alcohol (221 mg, 2.05 mmol) in DMA (1.5 ml) was added 60% sodium hydride (82 mg, 2.05 mmol). The mixture was stirred for 1 hour at ambient temperature. A solution of 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (534 mg, 2.05 mmol) in DMA (1.5 ml) was added and the mixture was stirred for 3 hours at ambient temperature. The mixture was diluted with 1N hydrochloric acid (10 ml) and extracted with ethyl acetate. The organic layer was evaporated and the residue was dissolved in THF (2 ml) and 6N hydrochloric acid (0.3 ml) was added. The mixture was stirred for 1 hour at ambient temperature and the solvents were removed under vacuum. The residue was partitioned

between ethyl acetate and water. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The solid was triturated with ether, filtered, washed with ether and dried under vacuum to give 3-acetylmethyl-1-benzyloxy-2-fluoro-4-nitrobenzene (350 mg, 56 %).

^{1}H NMR Spectrum: ($CDCl_3$) 2.35 (s, 3H) ; 4.25 (s, 2H) ; 5.25 (s, 2H) ; 7.0 (dd, 1H) ; 7.32-7.5 (m, 5H) ; 8.0 (dd, 1H)

A solution of 3-acetylmethyl-1-benzyloxy-2-fluoro-4-nitrobenzene (300 mg, 0.99 mmol) in ethanol (10 ml) and acetic acid (1 ml) containing 10 % palladium on charcoal (30 mg) was hydrogenated at 2 atmospheres pressure for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in ethyl acetate and the organic layer was washed with aqueous sodium hydrogen carbonate, brine and evaporated to give 4-fluoro-5-hydroxy-2-methylindole. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (3/7) to give 4-fluoro-5-hydroxy-2-methylindole (63 mg, 30%). Analytical data as above.

Alternatively the 4-fluoro-5-methoxy-2-methylindole can be prepared as follows:

A solution of sodium methoxide (freshly prepared from sodium (1.71g) and methanol (35ml)) was added to a solution of 1,2-difluoro-3-(2,2-dimethoxypropyl)-4-nitrobenzene (16.2 g, 62 mmol), (prepared as described above), in methanol (200ml) cooled at 5^0C. The mixture was left to warm to ambient temperature and was stirred for 3 days. The volatiles were removed under vacuum and the residue was partitioned between ethyl acetate and 2N hydrochloric acid (1ml). The organic layer was concentrated to a total volume of 100ml and THF (100ml) and 6N hydrochloric acid (25ml) were added. The mixture was stirred for 1 hour at ambient temperature. The volatiles were removed under vacuum and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (3/7) to give 3-acetylmethyl-2-fluoro-1-methoxy-4-nitrobenzene (12.7 g, 90%).

MS-ESI : 250 [MNa]+

^{1}H NMR Spectrum: ($CDCl_3$) 2.38 (s, 3H) ; 4.0 (s, 3H) ; 4.25 (s, 2H) ; 7.0 (dd, 1H) ; 8.05 (d, 1H)

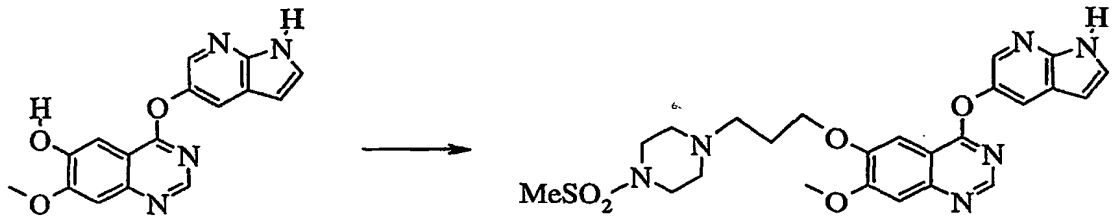
To a solution of 3-acetylmethyl-2-fluoro-1-methoxy-4-nitrobenzene (11.36g, 50 mmol) in acetone (200ml) was added 4M aqueous ammonium acetate (700ml) followed by a

solution of titanium trichloride (15% in water, 340ml) dropwise. The mixture was stirred for 10 minutes at ambient temperature and the mixture was extracted with ether. The organic layer was washed with 0.5N aqueous sodium hydroxide followed by water, brine, dried ($MgSO_4$) and the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with methylene chloride to give 4-fluoro-5-methoxy-2-methylindole (8.15g, 90%).

^1H NMR Spectrum: (DMSO) 2.35 (s, 3H) ; 3.8 (s, 3H) ; 6.1 (s, 1H) ; 6.85 (dd, 1H) ; 7.02 (d, 1H)

Cleavage of 4-fluoro-5-methoxy-2-methylindole with boron tribromide to give 4-fluoro-5-hydroxy-2-methylindole is described above.

Example 2



Diethyl azodicarboxylate (0.09g, 0.518mmol) was added dropwise to a solution of 4-(7-azaindol-5-yloxy)-6-hydroxy-7-methoxyquinazoline (0.133g, 0.432mmol), triphenylphosphine (0.17g, 0.647mmol) and 3-(4-methylsulphonylpiperazin-1-yl)propan-1-ol (0.115g, 0.519mmol) in DMF (4ml) and the mixture was stirred at ambient temperature for 1 hour. The volatiles were removed under vacuum and the residue was purified by column chromatography using increasingly polar mixtures of ethyl acetate and methylene chloride followed by methylene chloride and methanol. The fractions containing the expected product were combined and evaporated. The solid was then repurified by preparative LC/MS eluting with acetonitrile/water (containing 1% acetic acid). The fractions containing the expected product were combined and evaporated. The residue was dissolved in aqueous sodium hydrogen carbonate and methylene chloride. The organic phase was separated and dried over magnesium sulphate and evaporated. The residue was triturated under diethyl ether, filtered, washed with ether and dried under vacuum over P_2O_5 to give **4-(7-azaindol-5-yloxy)-7-methoxy-6-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline** (0.09, 40%).

NMR Spectrum ($DMSOd_6$, CF_3COOD) 2.3 (m, 2H), 3.05 (s, 3H), 3.1-3.3 (m, 4H), 3.4 (dd, 2H), 3.7 (d, 2H), 3.8 (d, 2H), 4.1 (s, 3H), 4.4 (dd, 2H), 6.6 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H), 7.8 (s, 1H), 8.1 (s, 1H), 8.3 (s, 1H), 9.0 (s, 1H)

Mass Spectrum : [M+H]+ 513

The starting material was prepared as follows:

Methanesulphonyl chloride (2.28ml) was added dropwise to a solution of 1-(*tert*-butoxycarbonyl)piperazine (5g) in methylene chloride (90ml) containing triethylamine (4.5ml). The solution was stirred at ambient temperature for 24 hours. The solution was poured onto cooled water and extracted with methylene chloride. The organic phase was separated, washed with brine and dried over magnesium sulphate and evaporated to give *tert*-butyl 4-(methylsulphonyl)piperazine-1-carboxylate (7g).

NMR Spectrum : ($CDCl_3$) 1.45 (s, 9H), 2.75 (s, 3H), 3.15 (m, 4H), 3.5 (m, 4H)

A solution of *tert*-butyl 4-(methylsulphonyl)piperazine-1-carboxylate (7g) in methylene chloride (150ml) containing TFA (35ml) was stirred for 2 hours at ambient temperature. The volatiles were removed under vacuum and the resultant residue was partitioned between methylene chloride and 2N aqueous sodium hydroxide. The organic phase was separated and washed with brine, dried over magnesium sulphate and evaporated to give 1-(methylsulphonyl)piperazine (2.18g).

NMR Spectrum : ($CDCl_3$) 2.9 (s, 3H), 3.0 (m, 4H), 3.2 (m, 2H)

A suspension of 1-(methylsulphonyl)piperazine (3g, 18.3mmol), 3-bromopropan-1-ol (3.3g, 23.8mmol) and potassium carbonate (3.28g, 23.8mmol) in acetonitrile (20ml) was stirred at 70^{0}C for 4 hours. After cooling, the mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography eluting with increasingly polar mixtures of methanol and methylene chloride to give 3-(4-methylsulphonylpiperazin-1-yl)propan-1-ol (2.93g, 72%).

NMR Spectrum ($CDCl_3$) 1.72 (m, 2H), 2.55-2.7 (m, 6H), 2.75 (s, 3H), 3.25 (m, 4H), 3.75 (dd, 2H)

Mass Spectrum [M+H]+ 223

A solution of 7-azaindole (20.0g, 169mmol) in ethanol (200ml) was treated with wet Raney Nickel (4g, 50% water) and stirred in a hydrogen atmosphere at 5 atmospheres pressure at 95^{0}C over 2 days. The reaction mixture was filtered through diatomaceous earth and the filtrate evaporated under vacuum. The residue was purified by column chromatography

eluting with ethyl acetate followed by increasingly polar mixtures of methylene chloride and methanol (saturated with ammonia) to give 7-azaindoline (12.1 g, 79%).

NMR spectrum : ($CDCl_3$) 3.06 (t, 2H), 3.61 (t, 2H), 4.48 (br s, 1H), 6.50 (m, 1H), 7.25 (m, 1H), 7.81 (d, 1H)

A solution of 7-azaindoline (22.7 g, 189 mmol), p-toluene sulphonic acid monohydrate (2.95 g, 15 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (27.4 g, 96 mmol) in methylene chloride (1500 ml) was stirred at ambient temperature for 3 hours. The reaction solution was then decanted from a black polymeric material; washed with 0.2 M sodium thiosulphate (4 x 250 mls) followed by brine and dried over magnesium sulphate. The filtrate was evaporated under vacuum to give a black solid which was extracted with boiling ethyl acetate (2 x 800 mls and 2 x 500 mls). The combined extracts were heated at reflux for a few minutes with decolourising charcoal, filtered and evaporated under vacuum to give 5-bromo-7-azaindoline (16.6 g, 44%).

NMR spectrum : ($CDCl_3$) 3.07 (t, 2H), 3.64 (t, 2H), 4.52 (s, 1H), 7.31 (d, 1H), 7.84 (d, 1H)

A mixture of 5-bromo-7-azaindoline (15.6g, 78 mmol) and precipitated, active manganese (IV) oxide (21.9 g, 252 mmol) in toluene (300 mls) was heated at 90^0C for 1 hour and the hot solution filtered through a pad of diatomaceous earth. The diatomaceous earth and manganese residues were washed with acetone and these washings added to the toluene filtrate. Evaporation of the filtrate under vacuum gave 5-bromo-7-azaindole (12.1 g, 78%).

NMR spectrum : ($CDCl_3$) 6.47 (m, 1H), 7.36 (m, 1H), 8.08 (d, 1H), 8.35 (d, 1H), 9.89 (s, 1H)

A solution of 5-bromo-7-azaindole (8.6 g, 44 mmol), copper (I) bromide (12.6 g, 88 mmol) and sodium methoxide (100 g, 1.85 mol) in a mixture of "degassed" DMF (260 mls) and methanol (175 mls) was stirred at ambient temperature in a nitrogen atmosphere, and then heated at reflux for 3.5 hours. The mixture was concentrated to about half its original volume, cooled in a cold water bath and treated dropwise with water causing an exotherm. The resulting suspension was evaporated under vacuum to give a brown solid which was then treated with water followed by ammonium hydroxide. The aqueous phase was extracted with ethyl acetate and the combined extracts were washed with dilute ammonium hydroxide until no blue colour was seen in the aqueous washings. The ethyl acetate solution was washed with brine, dried over $MgSO_4$, filtered and evaporated under vacuum. This crude solid, 5-methoxy-7-azaindole (6.3 g, 97%), was taken through the next step without further purification.

Boron tribromide (0.506µl, 5.35mmol) in methylene chloride (1ml) was added to a solution of 5-methoxy-7-azaindole (0.36g, 2.43mmol) in methylene chloride (25ml) cooled at -30^0C. The mixture was left to warm up to ambient temperature and was stirred overnight. The mixture was poured onto ice and water and the pH of the aqueous phase was adjusted to 6. The organic phase was separated and the aqueous phase was further extracted with ethyl acetate. The organic phases were combined, washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography eluting with increasingly polar mixtures of methylene chloride and methanol to give 5-hydroxy-7-azaindole (0.23g, 71%).

NMR Spectrum ($DMSOd_6$) 6.25 (s, 1H), 7.25 (s, 1H), 7.35 (s, 1H), 7.85 (s, 1H), 9.05 (br s, 1H)

Mass Spectrum [M+H]+ 135

A solution of 6-benzyloxy-4-chloro-7-methoxyquinazoline (0.449g, 1.49 mmol), (EP1153920 production examples 28-30), 5-hydroxy-7-azaindole (0.22g, 1.64mmol) and potassium carbonate (0.28g, 2.02 mmol) in DMF (5ml) was stirred at 95^0C for 3 hours. The mixture was filtered and the filtrate was evaporated and dried overnight under vacuum. The residue was triturated under methylene chloride and ethyl acetate and the solid was filtered and dried under vacuum to give 4-(7-azaindol-5-yloxy)-6-benzyloxy-7-methoxyquinazoline (0.36g, 60%).

NMR spectrum ($DMSOd_6$) : 4.05 (s, 3H), 5.35 (s, 2H), 6.5 (s, 1H), 7.35-7.5 (m, 4H), 7.5-7.6 (m, 3H), 7.8 (s, 1H), 7.95 (s, 1H), 8.2 (s, 1H), 8.55 (s, 1H)

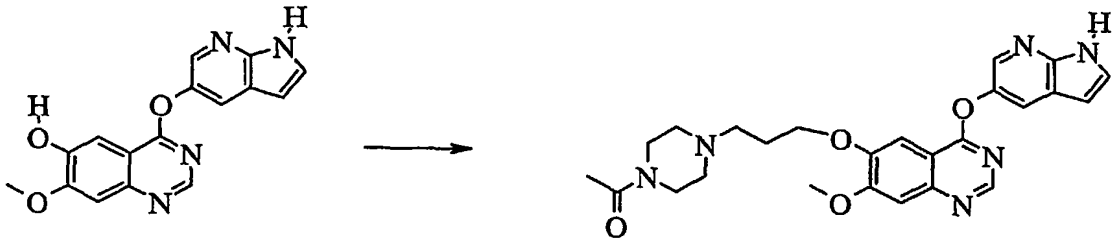
Mass spectrum : [M+H]+ 399

A solution of 4-(7-azaindol-5-yloxy)-6-benzyloxy-7-methoxyquinazoline (0.36g, 0.873 mmol), ammonium formate (0.55g, 8.73 mmol) and 10% palladium on carbon (0.05g) in DMF (7 ml) containing water (0.3ml) was stirred at ambient temperature for 1 hour. The mixture was filtered and the filtrate was evaporated. The residue was triturated under diethyl ether and the solid was filtered, washed with ether and dried under vacuum. The solid was triturated under water, filtered, washed with water and dried under vacuum over P_2O_5 to give 4-(7-azaindol-5-yloxy)-6-hydroxy-7-methoxyquinazoline (0.26g, 85%).

NMR spectrum ($DMSOd_6$) 4.05 (s, 3H), 6.5 (d, 1H), 7.4 (s, 1H),7.6 (m, 2H), 7.95 (s, 1H), 8.2 (s, 1H), 8.5 (s, 1H)

Mass Spectrum [M-H]- 307

Example 3



Using an analogous procedure to that described for the preparation of Example 2, 4-(7-azaindol-5-yloxy)-6-hydroxy-7-methoxyquinazoline (0.133g, 0.432mmol), (prepared as described for the starting material in Example 2), was reacted with 3-(4-acetylpiperazin-1-yl)propan-1-ol (0.097, 0.51mmol), (prepared as described for the starting material in Example 1), to give **6-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(7-azaindol-5-yloxy)-7-methoxyquinazoline** (0.11g, 53%).

NMR spectrum ($DMSOd_6$, CF_3 COOD)2.08 (s, 3H), 2.3 (m, 2H), 2.9-3.1 (m, 2H), 3.1-3.25 (m, 1H), 3.35 (dd, 2H), 3.45 (m, 1H), 3.6 (d, 2H), 4.0-4.05 (m, 1H), 4.1 (s, 3H), 4.4 (dd, 2H), 4.5 (d, 1H), 6.6 (d, 1H), 7.6 (s, 1H), 7.68 (d, 1H), 7.85 (s, 1H), 8.1 (s, 1H), 8.38 (s, 1H), 9.1 (s, 1H)

Mass Spectrum : [M+H]+ 477

Example 4

A solution of 7-(3-(4-acetylpiperazin-1-yl)propoxy)-4-chloro-6-methoxyquinazoline (0.285g, 0.753mmol), 5-hydroxy-7-azaindole (0.111g, 0.828mmol), (prepared as described for the starting material in Example 2), and potassium carbonate (0.114g, 0.828mmol) in DMF (1.6ml) was stirred and heated at 95^{0}C under nitrogen for 3 hours. The mixture was cooled and filtered and the filtrate was evaporated. The residue was purified by column chromatography eluting with increasingly polar mixtures of methylene chloride and methanol (saturated with ammonia). The fractions containing the expected product were combined and evaporated and the residue was triturated under diethyl ether, filtered and dried under vacuum to give **7-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(7-azaindol-5-yloxy)-6-methoxyquinazoline** (0.225g, 62%).

NMR Spectrum ($DMSOd_6$) 1.98 (s, 3H), 1.98 (m, 2H), 2.35 (dd, 2H), 2.4 (dd, 2H), 2.5 (m, 2H), 3.41 (m, 4H), 4.0 (s, 3H), 4.25 (dd, 2H), 6.47 (d, 1H), 7.38 (s, 1H), 7.55 (dd, 1H), 7.6 (s, 1H), 7.9 (d, 1H), 8.18 (d, 1H), 8.5 (s, 1H)

Mass spectrum : [M+H]+ 477.6

The starting material was prepared as follows :

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (10g, 0.04mol), (J. Med. Chem. 1977, vol 20, 146-149), and Gold's reagent (7.4g, 0.05mol) in dioxane (100ml) was stirred and heated at reflux for 24 hours. Sodium acetate (3.02g, 0.037mol) and acetic acid (1.65ml, 0.029mol) were added to the reaction mixture and it was heated for a further 3 hours. The mixture was evaporated, water was added to the residue, the solid was filtered off, washed with water and dried ($MgSO_4$). Recrystallisation from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

10% Palladium on carbon (8.3g) was added to a suspension of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (50 g, 0.177 mol) in dimethylformamide (800 ml) under nitrogen. Ammonium formate (111.8 g, 1.77 mol) was then added in portions over 5 minutes. The reaction mixture was stirred for one hour at ambient temperature then heated to 80°C for a further hour. The reaction mixture was filtered hot through diatomaceous earth and the residues washed with dimethylformamide. The filtrate was then concentrated and the residue suspended in water. The pH was adjusted to 7.0 using 2M sodium hydroxide and the resulting mixture was stirred at ambient temperature for one hour. The solid was filtered, washed with water and dried over phosphorus pentoxide yielding 7-hydroxy-6-methoxy-3,4-dihydroquinazolin-4-one as a white solid (20.52 g, 60%).

NMR spectrum: ($DMSOd_6$) 3.85 (s, 3H), 6.95 (s, 1H), 7.40 (s, 1H), 7.85 (s, 1H)

Mass spectrum : [M+H]+ 193.

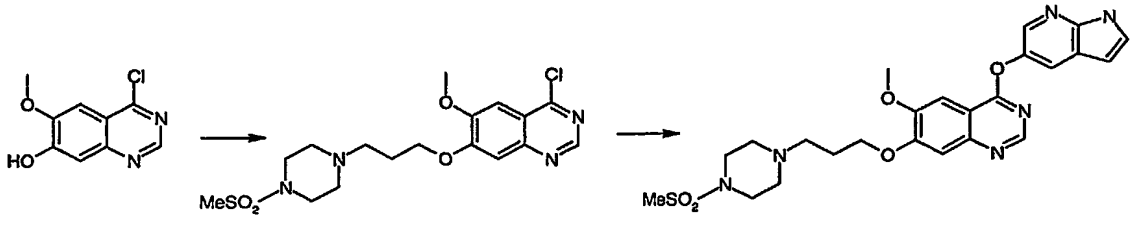
Pyridine (20 ml) was added to a suspension of 7-hydroxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.5 g, 107 mmol) in acetic anhydride (150 ml, 1.6 mol). The reaction mixture was heated to 120°C for three hours, during which time the solid dissolved. The reaction mixture was allowed to cool then poured into ice-water (900 ml). The reaction mixture was stirred for one hour then the solid was removed by filtration and dried over phosphorus pentoxide yielding 7-acetoxy-6-methoxy-3,4-dihydroquinazolin-4-one as a white solid (20.98 g, 84%).

NMR spectrum: ($DMSOd_6$) 2.25 (s, 3H), 3.85 (s, 3H), 7.40 (s, 1H), 7.60 (s, 1H), 8.00 (s, 1H)
Mass spectrum : [M+H]+ 235.

7-Acetoxy-6-methoxy-3,4-dihydroquinazolin-4-one (1 g, 4.3 mmol) was suspended in thionyl chloride (10.5 ml). One drop of dimethylformamide was added and the reaction was heated to 80°C for two hours, during which time the solid dissolved. The reaction mixture was cooled and the thionyl chloride was removed *in vacuo*. The residue was azeotroped with toluene before being suspended in methylene chloride. A solution of 10% ammonia in methanol (40 ml) was added and the reaction mixture was heated to 80°C for 15 minutes. After cooling the solvents were removed *in vacuo* and the residue redissolved in water (10 ml) and the pH adjusted to 7.0 with 2M hydrochloric acid. The resulting solid was filtered, washed with water and dried over phosphorus pentoxide yielding 4-chloro-7-hydroxy-6-methoxyquinazoline as a white solid (680 mg, 75%).
NMR spectrum: ($DMSOd_6$) 4.00 (s, 3H), 7.25 (s, 1H), 7.35 (s, 1H), 8.75 (s, 1H)
Mass spectrum : [M+H]+ 211-213

Diethyl azodicarboxylate (0.243g, 1.396mmol) was added dropwise to a solution of 4-chloro-7-hydroxy-6-methoxyquinazoline (0.245g, 1.16mmol), triphenylphosphine (0.396g, 1.51mmol) and 3-(4-acetylpiperazin-1-yl)propan-1-ol (0.238g, 1.28mmol), (prepared as described for the starting material in Example 1). After stirring at ambient temperature for 1 hour, the mixture was poured onto silica and eluted with increasingly polar mixtures of methylene chloride and methanol to give 7-(3-(4-acetylpiperazin-1-yl)propoxy)-4-chloro-6-methoxyquinazoline (0.29g, 66%).
NMR Spectrum ($DMSOd_6$) 2.0 (s, 3H), 2.0 (m, 2H), 2.35 (dd, 2H), 2.4 (dd, 2H), 2.5 (dd, 2H), 3.45 (m, 4H), 4.02 (s, 3H), 4.3 (dd, 2H), 7.4 (s,1H), 7.5 (s, 1H), 8.9 (s, 1H)
Mass spectrum : [M+H]+ 379-381.

Example 5



A suspension of 4-chloro-6-methoxy-7-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline (0.25g, 0.6mmol), 5-hydroxy-7-azaindole (0.089g, 0.663mmol),

(prepared as described for the starting material in Example 2), and potassium carbonate (0.091g, 0.66mmol) in DMF (3ml) was stirred at 85°C for 3 hours. The mixture was filtered and the filtrate was purified by preparative LC/MS eluting with acetonitrile/water (containing 1% acetic acid). The fractions containing the expected product were combined and evaporated. The residue was dissolved in methylene chloride and washed with 0.5N aqueous ammonia followed by brine, dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether, filtered and dried under vacuum to give **4-(7-azaindol-5-yloxy)-6-methoxy-7-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline** (0.138g, 45%).

NMR spectrum ($DMSOd_6$) 2.02 (m, 2H), 2.52 (m, 6H), 2.9 (s, 3H), 3.15 (m, 4H), 4.02 (s, 3H), 4.3 (dd, 2H), 6.5 (d, 1H), 7.4 (s, 1H), 7.6 (d, 1H), 7.65 (s, 1H), 7.95 (d, 1H), 8.2 (s, 1H), 8.52 (s, 1H)

Mass spectrum : [M+H]+ 513.5

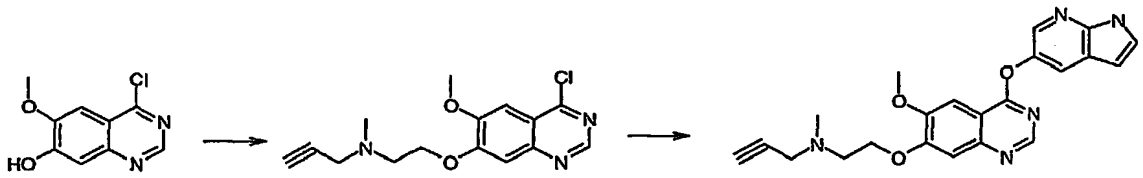
The starting material was prepared as follows :

Using an analogous procedure to that described for the preparation of the starting material in Example 4, 4-chloro-7-hydroxy-6-methoxyquinazoline (0.25g, 1.19mmol), (prepared as described for the starting material in Example 4), was reacted with 3-(4-methylsulphonylpiperazin-1-yl)propan-1-ol (0.29g, 1.3 mmol), (prepared as described in Example 2), to give 4-chloro-6-methoxy-7-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline (0.339g, 69%).

NMR spectrum ($DMSOd_6$) 2.0 (m, 2H), 2.5 (m, 6H), 2.85 (s, 3H), 3.1 (m 4H), 4.0 (s, 3H), 4.3 (dd, 2H), 7.4 (s, 1H), 7.42 (s, 1H), 8.85 (s, 1H)

Mass Spectrum : [M+H]+ 415-417

Example 6



Using an analogous procedure to that described for the preparation of Example 5, 4-chloro-6-methoxy-7-[2-(*N*-methyl-*N*-prop-2-yn-1-ylamino)ethoxy]quinazoline (0.25g, 0.817mmol) was reacted with 5-hydroxy-7-azaindole (0.12g, 0.899mmol), (prepared as

described for the starting material in Example 2), to give **4-(7-azaindol-5-yloxy)-6-methoxy-7-[2-(*N*-methyl-*N*-prop-2-yn-1-ylamino)ethoxy]quinazoline** (0.156g, 47%).

NMR spectrum ($DMSOd_6$) 2.35 (s, 3H), 2.9 (dd, 2H), 3.2 (dd, 1H), 3.45 (d, 2H), 4.02 (s, 3H), 4.31 (dd, 2H), 6.5 (d, 1H), 7.45 (s, 1H), 7.6 (dd, 1H), 7.65 (s, 1H), 7.95 (d, 1H), 8.2 (d, 1H), 8.52 (s, 1H)

Mass spectrum : [M+H]+ 404.

The starting material was prepared as follows:

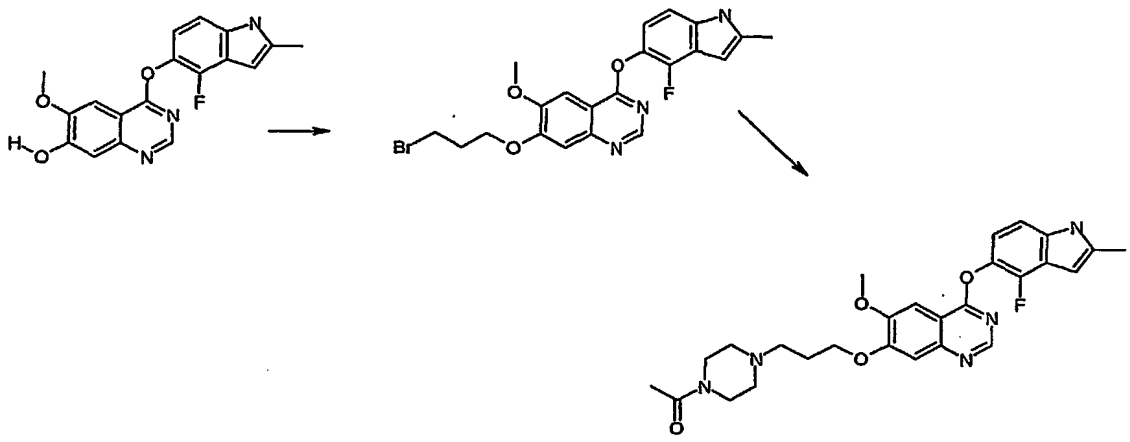
6N Aqueous sodium hydroxide (4.2ml) was added to a solution of 2-(methylamino)ethanol (1.42g, 18.9mmol), propargyl bromide in toluene (1.5g, 12.6mmol; 1.6ml) in dioxane (8ml). After stirring overnight at ambient temperature, the mixture was partitioned between water and ethyl acetate. The organic phase was separated, washed with brine, dried with magnesium sulphate and evaporated. The residue was purified by column chromatography eluting with increasingly polar mixtures of methylene chloride and methanol to give 2-(*N*-methyl-*N*-prop-2-yn-1-ylamino)ethanol (0.794g, 56%).

NMR spectrum ($CDCl_3$) 2.2 (dd, 1H), 2.3 (s, 3H), 2.58 (dd, 2H), 3.35 (d, 2H), 3.6 (dd, 2H)

Diethyl azodicarboxylate (0.297g, 1.71mmol) was added to a solution of 4-chloro-7-hydroxy-6-methoxyquinazoline (0.3g, 1.42mmol), (prepared as described for the starting material in Example 4), triphenylphosphine (0.485g, 1.85mmol) and 2-(*N*-methyl-*N*-prop-2-yn-1-ylamino)ethanol (0.177g, 1.56mmol) in methylene chloride (8ml). The mixture was stirred for 2 hours at ambient temperature and poured onto a column of silica and eluted with increasingly polar mixtures of methylene chloride and ethyl acetate followed by ethyl acetate to give 4-chloro-6-methoxy-7-[2-(*N*-methyl-*N*-prop-2-yn-1-ylamino)ethoxy]quinazoline (0.341g, 78%).

NMR Spectrum ($DMSOd_6$) 2.33 (s, 3H), 2.87 (t, 2H), 3.17 (t, 1H), 3.44 (d, 2H), 4.02 (s, 3H), 4.33 (t, 2H), 7.41 (s, 1H), 7.51 (s, 1H), 8.89 (s, 1H)

Example 7



A solution of 7-(3-bromopropoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline (0.25g, 0.543mmol) and 1-acetylpiperazine (0.208g, 1.63mmol) in DMF (4ml) was stirred at 80°C for 2.5 hours. The volatiles were removed under vacuum and the residue was purified by colum chromatography eluting with increasingly polar mixtures of methylene chloride and methanol. The fractions containing the expected product were combined and evaporated. The residue was triturated under diethyl ether and the resulting solid was filtered, washed with diethyl ether and dried under vacuum to give **7-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline** (0.25g, 0.543mmol).

NMR spectrum ($DMSOd_6$) 1.98 (s, 3H), 2.0 (m, 2H), 2.4 (s, 3H), 2.4 (m, 4H), 2.55 (t, 2H), 3.45 (dd, 4H), 4.0 (s, 3H), 4.3 (t, 2H), 6.22 (s, 1H), 6.98 (dd, 1H), 7.15 (d, 1H), 7.4 (s, 1H), 7.62 (s, 1H), 8.48 (s, 1H), 10.98 (br s, 1H)

Mass Spectrum [M+H]+ 508

The starting material was prepared as follows:

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (2.82g, 0.01mol), (prepared as described for the starting material in Example 4), thionyl chloride (40ml) and DMF (0.28ml) was stirred and heated at reflux for 1 hour. The mixture was evaporated, the residue was taken up in toluene and evaporated to dryness to give 7-benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (3.45g).

7-Benzyloxy-4-chloro-6-methoxyquinazoline hydrochloride (3.35g) was dissolved in methylene chloride (250ml) and washed with aqueous sodium hydrogen carbonate until the pH of the aqueous solution was adjusted to pH8. The organic layer was washed with brine,

dried ($MgSO_4$) and evaporated to give 7-benzyloxy-4-chloro-6-methoxyquinazoline free base (2.9g, 96%).

A suspension of 7-benzyloxy-4-chloro-6-methoxyquinazoline free base (10g, 33.2 mmol), 4-fluoro-5-hydroxy2-methylindole (5.9g, 35.7 mmol), (prepared as described for the starting material in Example 1), and potassium carbonate (9.2g, 66.6 mmol) in NMP (100ml) was stirred at 95°C for 1 hour. After cooling, the mixture was partitioned between ethyl acetate and aqueous sodium hydrogen carbonate. The organic layer was separated, washed with brine and dried over magnesium sulphate and evaporated under vacuum. The residue was triturated under acetonitrile and the suspension was cooled. The precipitate was filtered and dried under vacuum to give 7-benzyloxy-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline (8.2g, 57%).

NMR spectrum ($DMSOd_6$) : 2.4 (s, 3H), 4.0 (s, 3H), 5.35 (s, 2H), 6.22 (s, 1H), 6.95 (dd, 1H), 7.15 (d, 1H), 7.3-7.55 (m, 6H), 7.51 (s, 1H), 8.5 (s, 1H)

A suspension of 7-benzyloxy-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline (8.2g, 19.1 mmol), ammonium formate (12g, 190 mmol) in DMF (50 ml) containing 10% palladium on carbon (2g) was stirred at ambient temperature for 1.5 hours. The mixture was diluted with ethyl acetate and filtered over diatomaceous earth. A solid precipitated out of the filtrate. The solid was filtered off. The filtrate was washed with aqueous sodium hydrogen carbonate, followed by brine and dried over magnesium sulphate. The volatiles were removed under vacuum. The residual solid was combined with the solid previously isolated from the filtrate and was then triturated with acetonitrile under cooling. The precipitate was filtered, washed with acetonitrile followed by diethyl ether and dried under vacuum to give 4-(4-fluoro-2-methylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (6.48g, quant.).

NMR Spectrum: ($DMSOd_6$) 2.4 (s, 3H), 3.98 (s, 3H), 6.22 (s, 1H), 6.95 (dd, 1H), 7.15 (d, 1H), 7.2 (s, 1H), 7.58 (s, 1H), 8.38 (s, 1H)

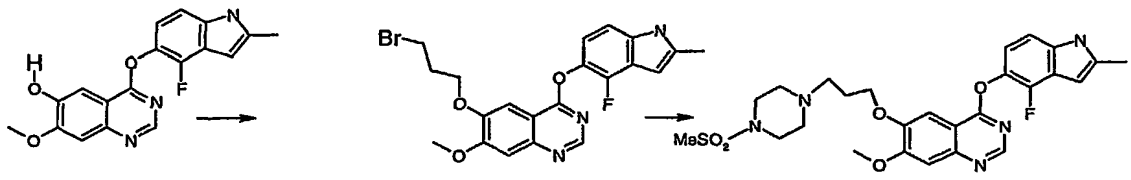
Diethyl azodicarboxylate (557µl, 3.53 mmol) was added to a solution of 4-(4-fluoro-2-methylindol-5-yloxy)-7-hydroxy-6-methoxyquinazoline (1g, 2.95mmol), triphenylphosphine (1.15g, 4.42mmol) and 3-bromo-1-propanol (293µl, 3.24mmol) in methylene chloride (25ml). The mixture was stirred at ambient temperature for 1 hour and the residue was purified by column chromatography eluting with increasingly polar mixtures of methylene chloride and methanol. The fractions containing the expected product were combined and evaporated. The residue was triturated under diethyl ether and the solid was filtered, washed with diethyl ether

and evaporated to give 7-(3-bromopropoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline (1.35g, 100%).

NMR Spectrum ($DMSOd_6$) 2.4 (m, 2H), 2.45 (s, 3H), 3.75 (dd, 2H), 4.05 (s, 3H), 4.35 (dd, 2H), 6.25 (s, 1H), 7.0 (dd, 1H), 7.2 (d, 1H), 7.45 (s, 1H), 7.65 (s, 1H), 8.55 (s, 1H), 9.0 (br s, 1H)

Mass Spectrum : [M+H]+ 460-462

Example 8



A solution of 6-(3-bromopropoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-7-methoxyquinazoline (0.3g, 0.652mmol) and 1-(methylsulphonyl)piperazine (0.322g, 1.95mmol), (prepared as described for the starting material in Example 2), in DMF (4ml) was stirred at 80°C for 2.5 hours. The volatiles were removed under vacuum and the residue was purified by column chromatography eluting with increasingly polar mixtures of methylene chloride and methanol. The fractions containing the expected product were combined and evaporated. The residue was triturated under diethyl ether and the resulting solid was filtered, washed with diethyl ether and dried under vacuum to give **4-(4-fluoro-2-methylindol-5-yloxy)-7-methoxy-6-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline** (0.08g, 23%).

NMR Spectrum ($DMSOd_6$ and CF_3COOD) 2.3 (m, 2H), 2.4 (s, 3H), 3.0 (s, 3H), 3.1-3.3 (m, 4H), 3.4 (dd, 2H), 3.7 (d, 2H), 3.8 (d, 2H), 4.1 (s, 3H), 4.4 (dd, 2H), 6.25 (s, 0.2H, partly exchanged), 7.0 (dd, 1H), 7.2 (d, 1H), 7.55 (s, 1H), 7.82 (s, 1H), 9.1 (s, 1H)

Mass Spectrum : [M+H]+ 544

The starting material was prepared as follows :

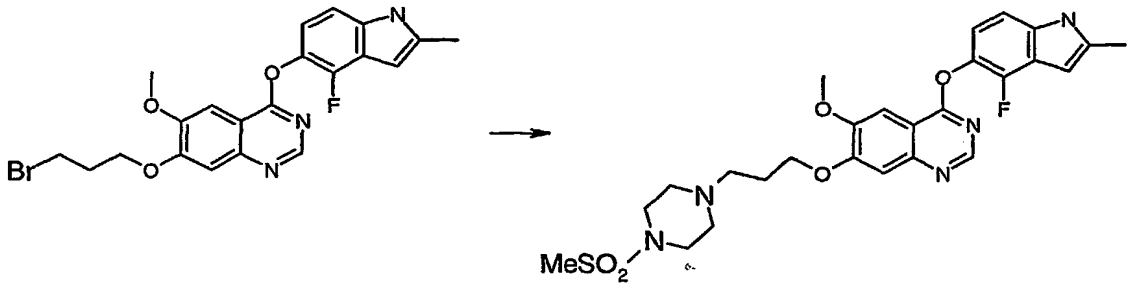
Diethyl azodicarboxylate (0.847g, 4.86mmol) was added to a solution of 4-(4-fluoro-2-methylindol-5-yloxy)-6-hydroxy-7-methoxyquinazoline (1.5g, 4.42mmol), (prepared as described for the starting material in Example 1), triphenylphosphine (1.74g, 6.63mmol) and 3-bromo-1-propanol (0.923g, 6.63mmol) in methylene chloride. After stirring for 1 hour at

ambient temperature, triphenylphosphine (1.16g) and DEAD (0.770g) was added. After stirring for 30 minutes, the volatiles were removed under vacuum and the residue was purified by column chromatograhy eluting with increasingly polar mixtures of methylene chloride and ethyl acetate to give 6-(3-bromopropoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-7-methoxyquinazoline (1.5g, 73%).

NMR Spectrum ($DMSOd_6$) 2.4 (m, 2H), 2.45 (s, 3H), 3.75 (dd, 2H), 4.05 (s, 3H), 4.32 (dd, 2H), 6.25 (s, 1H), 7.02 (dd, 2H), 7.18 (d, 1H), 7.42 (s, 1H), 7.7 (s, 1H)8.55 (s, 1H)

Mass Spectrum : [M+H]+ 460-462

Example 9

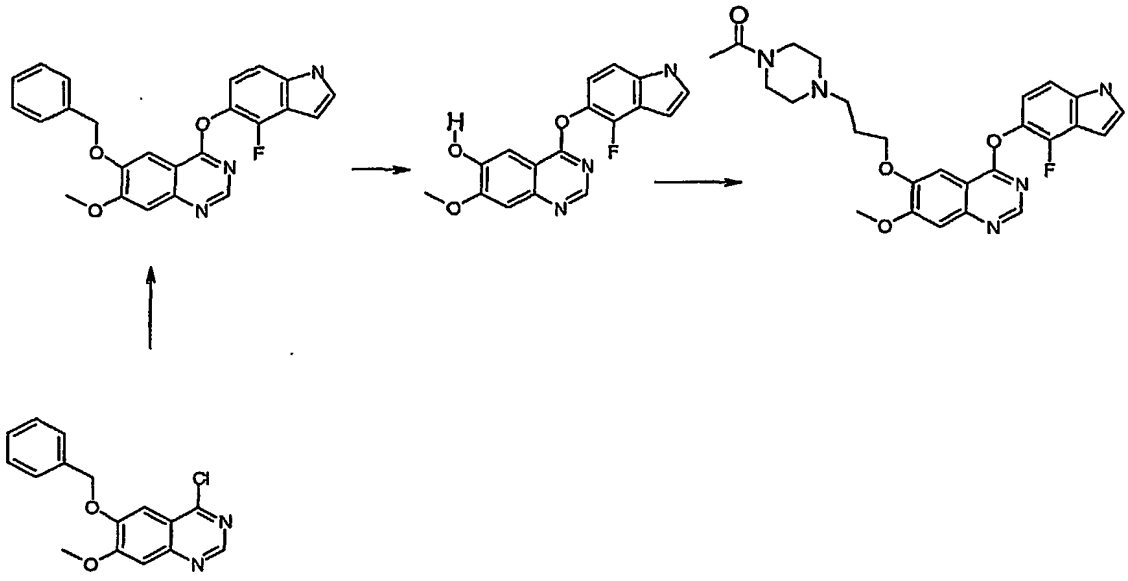


Using an analogous procedure to that described for the preparation of Example 8, 7-(3-bromopropoxy)-4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxyquinazoline (0.25g, 0.54mmol), (prepared as described for the starting material in Example 7), was reacted with 1-methylsulphonylpiperazine (0.268g, 163mmol), (prepared as described for the starting material in Example 2), in DMF to give **4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(4-methylsulphonylpiperazin-1-yl)propoxy)quinazoline** (0.14g, 47%).

NMR spectrum ($DMSOd_6$, CF_3COOD) 2.35 (m, 2H), 2.4 (s, 3H), 3.02 (s, 3H), 3.1-3.3 (m, 4H), 3.4 (dd, 2H), 3.7 (d, 2H), 3.8 (d, 2H), 4.08 (s, 3H), 4.4 (dd, 2H), 6.25 (s, 0.2H, partly exchanged), 7.0 (dd, 1H), 7.2 (d, 1H), 7.58 (s, 1H), 7.82 (s, 1H), 9.1 (s, 1H)

Mass spectrum [M+H]+ 544

Example 10



Diethyl azodicarboxylate (117µl, 0.738mmol) was added dropwise to a solution of 4-(4-fluoroindol-5-yloxy)-6-hydroxy-7-methoxyquinazoline (0.2g, 0.615mmol), triphenylphosphine (0.242g, 0.92mmol) and 3-(4-acetylpiperazin-1-yl)propan-1-ol (0.137g, 0.738mmol), (prepared as described for the starting material in Example 1), in methylene chloride (5ml). After stirring at ambient temperature for 1 hour, triphenylphosphine (0.032g), 3-(4-acetylpiperazin-1-yl)propan-1-ol (0.022g) and diethyl azodicarboxylate (20µl) were added. The mixture was stirred for 1 hour at ambient temperature and evaporated under vacuum. The residue was purified by column chromatography, eluting with increasingly polar mixtures of methylene chloride and ethyl acetate followed by methylene chloride and methanol. The fractions containing the expected product were combined and evaporated. The residue was repurified by preparative LC/MS eluting with increasingly polar mixtures of acetonitrile and water (containing 1% acetic acid). The fractions containing the expected product were combined and evaporated. The residue was triturated under diethyl ether and pentane and the residue was filtered, washed with diethyl ether and dried under vacuum to give **6-(3-(4-acetylpiperazin-1-yl)propoxy)-4-(4-fluoroindol-5-yloxy)-7-methoxyquinazoline** (0.057g, 19%).

NMR spectrum ($DMSOd_6$, CF_3COOD) 2.05 (s, 3H), 2.3 (m, 2H), 2.9-3.1 (m, 2H), 3.15 (m, 1H), 3.35 (dd, 2H), 3.45 (m, 1H), 3.6 (d, 2H), 4.05 (m, 1H), 4.1 (s, 3H), 4.4 (dd, 2H), 4.5 (d, 1H), 6.55 (d, 1H), 7.15 (dd, 1H), 7.38 (d, 1H), 7.5 (d, 1H), 7.58 (s, 1H), 7.85 (s, 1H), 9.12 (s, 1H)

Mass Spectrum : [M+H]+ 494

The starting material was prepared as follows :

A mixture of 6-benzyloxy-4-chloro-7-methoxyquinazoline (0.88g, 2.9mmol), (EP1153920 production examples 28-30), 4-fluoro-5-hydroxyindole (0.53g, 3.5mmol) and potassium carbonate (0.607g, 4.39mmol) in DMF (18ml) was stirred at 95^{0}C for 2 hours. After cooling, the mixture was filtered and the volatiles were removed under vacuum. The residue was purified by column chromatography eluting with increasingly polar mixtures of methylene chloride and ethyl acetate to give 6-benzyloxy-4-(4-fluoroindol-5-yloxy)-7-methoxyquinazoline (0.8g, 67%).

NMR spectrum ($DMSOd_6$) 4.05 (s, 3H), 5.35 (s, 2H), 6.6 (s, 1H), 7.1 (dd, 1H), 7.35 (d, 1H), 7.35-7.5 (m, 5H), 7.55 (d, 2H), 7.8 (s, 1H), 8.55 (s, 1H), 11.5 (br s, 1H)

Mass spectrum [M+H]+ 416

6-Benzyloxy-4-(4-fluoroindol-5-yloxy)-7-methoxyquinazoline (0.75g, 1.8mmol), ammonium formate (1.14g, 18mmol) and 10% palladium on carbon (115mg) in DMF (8ml) containing water (1.5ml) was stirred at ambient temperature for 2.5 hours. The mixture was filtered over diatomaceous earth and the filtrate was evaporated. The residue was triturated under diethyl ether, filtered, washed with water, followed by diethyl ether and dried overnight over P_2O_5 to give 4-(4-fluoroindol-5-yloxy)-6-hydroxy-7-methoxyquinazoline (0.471g, 80%).

NMR Spectrum ($DMSOd_6$)4.02 (s, 3H), 6.55 (s, 1H), 7.1 (dd, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.5 (dd, 1H), 7.6 (s, 1H), 8.48 (s, 1H)

Mass Spectrum [M+H]+ 326

A mixture of 2-fluoro-4-nitrophenol (15gr, 95.5 mmol) and benzyl bromide (18g, 105 mmol) in acetone (125 ml) containing potassium carbonate (26.5 gr, 190 mmol) was heated at reflux for 2 hours. The volatiles were removed and the residue was partitioned between 2N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and the volatiles were removed under vacuum. The solid was triturated with petroleum ether to give 2-fluoro-4-nitro-benzyloxybenzene (23g, 97%).

^{1}H NMR Spectrum: ($CDCl_3$) 5.3 (s, 2H) ; 7.1 (t, 1H) ; 7.35-7.55 (m, 5H) ; 8.0(m, 2H)

To a solution of potassium *tert*-butoxide (1.72g, 15.4 mmol) in DMF (15 ml) cooled at -30^{0}C, was added dropwise a solution of 2-fluoro-4-nitro-benzyloxybenzene (1.73g, 7 mmol) and 4-chlorophenoxyacetonitrile (1.29 g, 7.7 mmol) while maintaining the temperature below

-25°C. After completion of addition, the mixture was stirred for 30 minutes at -20°C and then poured onto a mixture of cold 1N hydrochloric acid and ether. The organic layer was separated, washed with 1N sodium hydroxide, followed by water, brine, dried ($MgSO_4$). The volatiles were removed under vacuum and the residue was purified by column chromatography eluting with methylene chloride/petroleum ether (3/1) to give a mixture of 3-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene and 5-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene (1.2 g, 60%).

^{1}H NMR Spectrum: ($DMSOd_6$) 4.22 (s, 2H, 3-cyanomethyl isomer) ; 4.3 (s, 2H, 5-cyanomethyl isomer); 5.32 (s, 2H, 5-cyanomethyl isomer) ; 5.36 (s, 2H, 3-cyanomethyl isomer); 7.3-7.7 (m, 6H); 8.1 (d, 1H, 3-cyanomethyl isomer); 8.2 (d, 1H, 5-cyanomethyl isomer)

A solution of a mixture of 3-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene and 5-cyanomethyl-2-fluoro-4-nitrobenzyloxybenzene (23g, 80.4 mmol) in ethanol (220ml) and acetic acid (30ml) containing 10% palladium on charcoal (600mg) was hydrogenated under 3 atmospheres pressure until hydrogen uptake ceased. The mixture was filtered and the filtrate was evaporated under vacuum. The residue was purified on column chromatography using a Prochrom® equipment eluting with methylene chloride/petroleum ether (20/80) to give 4-fluoro-5-hydroxyindole (2.48g) and 6-fluoro-5-hydroxyindole (3.5 g).

4-fluoro-5-hydroxyindole:

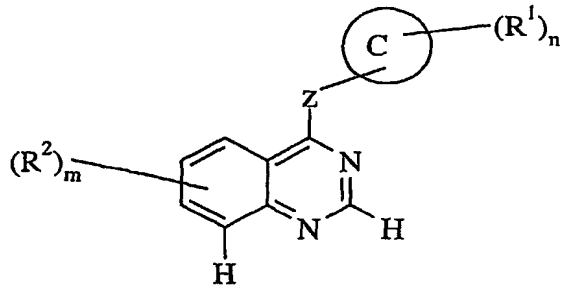
^{1}H NMR Spectrum: ($DMSOd_6$) 6.32 (s, 1H) ; 6.75 (dd, 1H) ; 7.0 (d, 1H) ; 7.28 (dd, 1H) ; 8.8 (br s, 1H) ; 11.05 (br s, 1H)

6-fluoro-5-hydroxyindole:

^{1}H NMR Spectrum: ($DMSOd_6$) 6.25 (s, 1H) ; 7.0 (d, 1H) ; 7.12 (d, 1H) ; 7.2 (dd, 1H) ; 9.0 (br s, 1H)

Claims:

1. Use of a compound of the formula I:



(I)

wherein:

ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which moiety may be saturated or unsaturated, which may be aromatic or non-aromatic, and which optionally may contain 1-3 heteroatoms selected independently from O, N and S;

Z is -O-, -NH- or -S-;

n is 0, 1, 2, 3, 4 or 5;

m is 0, 1, 2 or 3;

R^2 represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl, $-NR^3R^4$ (wherein R^3 and R^4, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or R^5X^1- (wherein X^1 represents a direct bond, -O-, -CH_2-, -OC(O)-, -C(O)-, -S-, -SO-, -SO_2-, $-NR^6C(O)$-, $-C(O)NR^7$-, $-SO_2NR^8$-, $-NR^9SO_2$- or $-NR^{10}$- (wherein R^6, R^7, R^8, R^9 and R^{10} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^5 is selected from one of the following twenty-two groups:

1) hydrogen, oxiranylC_{1-4}alkyl or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) C_{1-5}alkyl$X^2C(O)R^{11}$ (wherein X^2 represents -O- or $-NR^{12}$- (in which R^{12} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{11} represents C_{1-3}alkyl, $-NR^{13}R^{14}$ or $-OR^{15}$ (wherein R^{13}, R^{14} and R^{15} which may be the same or different each represents hydrogen, C_{1-5}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{16} (wherein X^3 represents -O-, -S-, -SO-, -SO_2-, -OC(O)-, $-NR^{17}C(O)$-, $-C(O)NR^{18}$-, $-SO_2NR^{19}$-, $-NR^{20}SO_2$- or $-NR^{21}$- (wherein R^{17}, R^{18}, R^{19}, R^{20} and R^{21} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} represents

hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{22} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, -SO_2-, -$NR^{23}C(O)$-, -$C(O)NR^{24}$-, -SO_2NR^{25}-, -$NR^{26}SO_2$- or -NR^{27}- (wherein R^{23}, R^{24}, R^{25}, R^{26} and R^{27} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{22} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

5) R^{28} (wherein R^{28} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

6) C_{1-5}alkylR^{28} (wherein R^{28} is as defined herein);

7) C_{2-5}alkenylR^{28} (wherein R^{28} is as defined herein);

8) C_{2-5}alkynylR^{28} (wherein R^{28} is as defined herein);

9) R^{29} (wherein R^{29} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from oxo, hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -

$C(O)NR^{30}R^{31}$, $-NR^{32}C(O)R^{33}$ (wherein R^{30}, R^{31}, R^{32} and R^{33}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and a group $-(-O-)_f(C_{1-4}alkyl)_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

10) C_{1-5}alkylR^{29} (wherein R^{29} is as defined herein);

11) C_{2-5}alkenylR^{29} (wherein R^{29} is as defined herein);

12) C_{2-5}alkynylR^{29} (wherein R^{29} is as defined herein);

13) C_{1-5}alkylX^6R^{29} (wherein X^6 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{34}C(O)-$, $-C(O)NR^{35}-$, $-SO_2NR^{36}-$, $-NR^{37}SO_2-$ or $-NR^{38}-$ (wherein R^{34}, R^{35}, R^{36}, R^{37} and R^{38} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined herein);

14) C_{2-5}alkenylX^7R^{29} (wherein X^7 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{39}C(O)-$, $-C(O)NR^{40}-$, $-SO_2NR^{41}-$, $-NR^{42}SO_2-$ or $-NR^{43}-$ (wherein R^{39}, R^{40}, R^{41}, R^{42} and R^{43} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined herein);

15) C_{2-5}alkynylX^8R^{29} (wherein X^8 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{44}C(O)-$, $-C(O)NR^{45}-$, $-SO_2NR^{46}-$, $-NR^{47}SO_2-$ or $-NR^{48}-$ (wherein R^{44}, R^{45}, R^{46}, R^{47} and R^{48} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined herein);

16) C_{1-4}alkylX^9C_{1-4}alkylR^{29} (wherein X^9 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{49}C(O)-$, $-C(O)NR^{50}-$, $-SO_2NR^{51}-$, $-NR^{52}SO_2-$ or $-NR^{53}-$ (wherein R^{49}, R^{50}, R^{51}, R^{52} and R^{53} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{29} is as defined herein);

17) C_{1-4}alkylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined herein);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined herein);

21) C_{2-5}alkynylX^9C_{1-4}alkylR^{28} (wherein X^9 and R^{28} are as defined herein); and

22) C_{1-4}alkyl$R^{54}(C_{1-4}alkyl)_q(X^9)_rR^{55}$ (wherein X^9 is as defined herein, q is 0 or 1, r is 0 or 1, and R^{54} and R^{55} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected

independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the proviso that R^{54} cannot be hydrogen);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in R^5X^1- which is linked to X^1 may bear one or more substituents selected from hydroxy, halogeno and amino);

R^1 represents hydrogen, oxo, halogeno, hydroxy, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkoxymethyl, C_{1-4}alkanoyl, C_{1-4}haloalkyl, cyano, amino, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-3}alkanoyloxy, nitro, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, N-C_{1-4}alkylcarbamoyl, N,N-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di(C_{1-4}alkyl)aminosulphonyl, N-(C_{1-4}alkylsulphonyl)amino, N-(C_{1-4}alkylsulphonyl)-N-(C_{1-4}alkyl)amino, N,N-di(C_{1-4}alkylsulphonyl)amino, a C_{3-7}alkylene chain joined to two ring C carbon atoms, C_{1-4}alkanoylaminoC_{1-4}alkyl, carboxy or a group $R^{56}X^{10}$ (wherein X^{10} represents a direct bond, -O-, -CH_2-, -OC(O)-, -C(O)-, -S-, -SO-, -SO_2-, -NR^{57}C(O)-, -C(O)NR^{58}-, -SO_2NR^{59}-, -$NR^{60}SO_2$- or -NR^{61}- (wherein R^{57}, R^{58}, R^{59}, R^{60} and R^{61} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^{56} is selected from one of the following twenty-two groups:

1) hydrogen, oxiranylC_{1-4}alkyl or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;

2) C_{1-5}alkylX^{11}C(O)R^{62} (wherein X^{11} represents -O- or -NR^{63}- (in which R^{63} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{62} represents C_{1-3}alkyl, -$NR^{64}R^{65}$ or -OR^{66} (wherein R^{64}, R^{65} and R^{66} which may be the same or different each represents hydrogen, C_{1-5}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkyl$X^{12}R^{67}$ (wherein X^{12} represents -O-, -S-, -SO-, -SO_2-, -OC(O)-, -NR^{68}C(O)-, -C(O)NR^{69}-, -SO_2NR^{70}-, -$NR^{71}SO_2$- or -NR^{72}- (wherein R^{68}, R^{69}, R^{70}, R^{71} and R^{72} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{67} represents

hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

4) C_{1-5}alkyl$X^{13}C_{1-5}$alkyl$X^{14}R^{73}$ (wherein X^{13} and X^{14} which may be the same or different are each -O-, -S-, -SO-, -SO_2-, -NR^{74}C(O)-, -C(O)NR^{75}-, -SO_2NR^{76}-, -$NR^{77}SO_2$- or -NR^{78}- (wherein R^{74}, R^{75}, R^{76}, R^{77} and R^{78} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{73} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);

5) R^{79} (wherein R^{79} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

6) C_{1-5}alkylR^{79} (wherein R^{79} is as defined herein);

7) C_{2-5}alkenylR^{79} (wherein R^{79} is as defined herein);

8) C_{2-5}alkynylR^{79} (wherein R^{79} is as defined herein);

9) R^{80} (wherein R^{80} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from oxo, hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -

$C(O)NR^{81}R^{82}$, $-NR^{83}C(O)R^{84}$ (wherein R^{81}, R^{82}, R^{83} and R^{84}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and a group $-(-O-)_f(C_{1-4}alkyl)_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

10) C_{1-5}alkylR^{80} (wherein R^{80} is as defined herein);

11) C_{2-5}alkenylR^{80} (wherein R^{80} is as defined herein);

12) C_{2-5}alkynylR^{80} (wherein R^{80} is as defined herein);

13) C_{1-5}alkyl$X^{15}R^{80}$ (wherein X^{15} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{85}C(O)-$, $-C(O)NR^{86}-$, $-SO_2NR^{87}-$, $-NR^{88}SO_2-$ or $-NR^{89}-$ (wherein R^{85}, R^{86}, R^{87}, R^{88} and R^{89} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined herein);

14) C_{2-5}alkenyl$X^{16}R^{80}$ (wherein X^{16} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{90}C(O)-$, $-C(O)NR^{91}-$, $-SO_2NR^{92}-$, $-NR^{93}SO_2-$ or $-NR^{94}-$ (wherein R^{90}, R^{91}, R^{92}, R^{93} and R^{94} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined herein);

15) C_{2-5}alkynyl$X^{17}R^{80}$ (wherein X^{17} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{95}C(O)-$, $-C(O)NR^{96}-$, $-SO_2NR^{97}-$, $-NR^{98}SO_2-$ or $-NR^{99}-$ (wherein R^{95}, R^{96}, R^{97}, R^{98} and R^{99} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined herein);

16) C_{1-4}alkyl$X^{18}C_{1-4}$alkylR^{80} (wherein X^{18} represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{100}C(O)-$, $-C(O)NR^{101}-$, $-SO_2NR^{102}-$, $-NR^{103}SO_2-$ or $-NR^{104}-$ (wherein R^{100}, R^{101}, R^{102}, R^{103} and R^{104} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{80} is as defined herein);

17) C_{1-4}alkyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined herein);

18) C_{2-5}alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

19) C_{2-5}alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C_{1-4}alkylamino, N,N-di(C_{1-4}alkyl)amino, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl and N,N-di(C_{1-4}alkyl)aminosulphonyl;

20) C_{2-5}alkenyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined herein);

21) C_{2-5}alkynyl$X^{18}C_{1-4}$alkylR^{79} (wherein X^{18} and R^{79} are as defined herein); and

22) C_{1-4}alkyl$R^{105}(C_{1-4}alkyl)_x(X^{18})_yR^{106}$ (wherein X^{18} is as defined herein, x is 0 or 1, y is 0 or 1, and R^{105} and R^{106} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected

independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl) with the proviso that R^{105} cannot be hydrogen);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in $R^{56}X^{10}$- which is linked to X^{10} may bear one or more substituents selected from hydroxy, halogeno and amino);

with the proviso that one or more R^1 and/or one or more R^2 are selected from one of the following three groups:

(i) Q^1X^1-

wherein X^1 is as defined herein and Q^1 is selected from one of the following nine groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, C_{1-6}fluoroalkanoyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, C_{1-6}fluoroalkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl));

2) C_{1-5}alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, -SO_2-, -OC(O)-, -NQ^3C(O)-, -C(O)NQ^4-, -SO_2NQ^5-, -NQ^6SO_2- or –NQ^7- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each

independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined herein;

3) C_{1-5}alkylQ^2 (wherein Q^2 is as defined herein);

4) C_{2-5}alkenylQ^2 (wherein Q^2 is as defined herein);

5) C_{2-5}alkynylQ^2 (wherein Q^2 is as defined herein);

6) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, $-SO_2-$, $-NQ^8C(O)-$, $-C(O)NQ^9-$, $-SO_2NQ^{10}-$, $-NQ^{11}SO_2-$ or $-NQ^{12}-$ (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined herein);

7) C_{2-5}alkenylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined herein);

8) C_{2-5}alkynylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined herein); and

9) C_{1-4}alkyl$Q^{13}(C_{1-4}$alkyl$)_j(W^2)_kQ^{14}$ (wherein W^2 is as defined herein, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, C_{1-6}fluoroalkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group $-(-O-)_f(C_{1-4}$alkyl$)_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the provisos that Q^{13} cannot be hydrogen and one or both of Q^{13} and Q^{14} must be a 5-6-membered saturated or partially unsaturated heterocyclic group as defined herein which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, C_{1-6}fluoroalkanoyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group optionally bears 1 or 2 further substituents selected from those defined herein);

and additionally wherein any C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl group in Q^1X^1- which is linked to X^1 may bear one or more substituents selected from hydroxy, halogeno and amino);

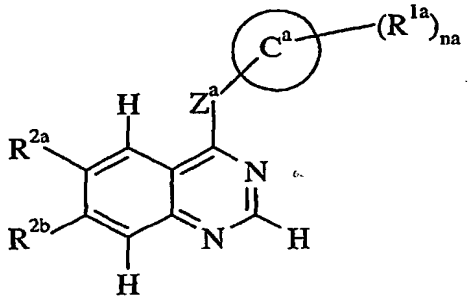
(ii) $Q^{15}W^3-$

wherein W^3 represents $-NQ^{16}C(O)-$, $-C(O)NQ^{17}-$, $-SO_2NQ^{18}-$, $-NQ^{19}SO_2-$ or $-NQ^{20}-$ (wherein Q^{16}, Q^{17}, Q^{18}, Q^{19} and Q^{20} each independently represents C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}haloalkyl), and Q^{15} is C_{1-6}haloalkyl, C_{2-5}alkenyl or C_{2-5}alkynyl; and

(iii) $Q^{21}W^4C_{1-5}$alkylX^1- wherein W^4 represents $-NQ^{22}C(O)-$, $-C(O)NQ^{23}-$, $-SO_2NQ^{24}-$, $-NQ^{25}SO_2-$ or $-NQ^{26}-$ (wherein Q^{22}, Q^{23}, Q^{24}, Q^{25} and Q^{26} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl), and Q^{21} represents C_{1-6}haloalkyl, C_{2-5}alkenyl or C_{2-5}alkynyl, and X^1 is as defined herein;

or a salt thereof, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

2. A compound of the formula II:



(II)

[wherein:

ring C^a is indolyl, indazolyl or azaindolyl;

R^{1a} is selected from oxo, hydroxy, C_{1-2}alkoxymethyl, amino, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, cyano, nitro, C_{1-3}alkanoyl,

(i) Q^1X^1 wherein Q^1 and X^1 are as defined in claim 1;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined in claim 1; and

(iii) $Q^{21}W^4C_{1-5}$alkylX^1- wherein Q^{21}, W^4 and X^1 are as defined in claim 1;

R^{2a} and R^{2b}, are each independently selected from hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylsulphanyl, $-NR^{3a}R^{4a}$ (wherein R^{3a} and R^{4a}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl),

(i) Q^1X^1 wherein Q^1 and X^1 are as defined in claim 1;

(ii) $Q^{15}W^3$ wherein Q^{15} and W^3 are as defined in claim 1; and

(iii) $Q^{21}W^4C_{1-5}alkylX^1$- wherein Q^{21}, W^4 and X^1 are as defined in claim 1;

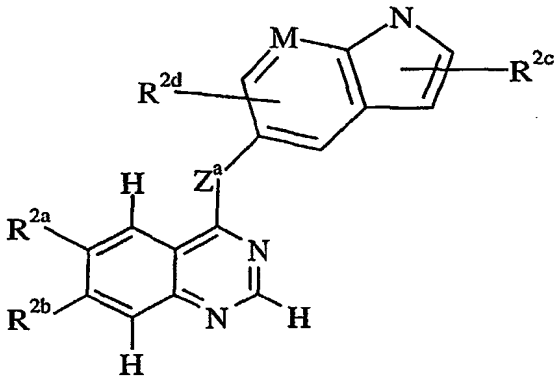
Z^a is -O- or -S-;

and na is 0, 1 or 2;

with the proviso that at least one of R^{2a} and R^{2b} is selected from (i), (ii) and (iii) as defined herein and/or R^{1a} is selected from (i), (ii) and (iii) as defined herein;

or a salt thereof.

3. A compound as claimed in claim 2 of the formula IIa:



(IIa)

[wherein:

M is -CH- or -N-;

R^{2c} is linked to a carbon atom of the 5-membered ring and is selected from hydrogen and methyl;

R^{2d} is linked to a carbon atom of the 6-membered ring and is selected from hydrogen and fluoro;

Z^a, R^{2a} and R^{2b}, are as defined in claim 2;

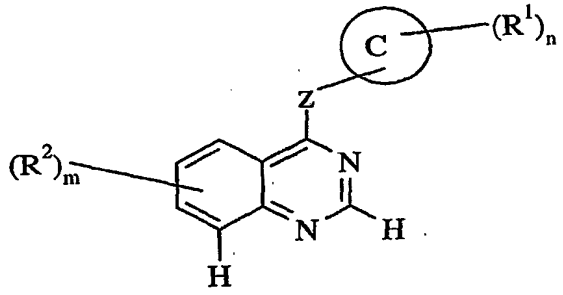
with the proviso that at least one of R^{2a} and R^{2b} is selected from (i), (ii) and (iii) as defined in claim 2;

or a salt thereof.

A B S T R A C T

TITLE: Chemical Compounds

The invention relates to the use of compounds of the formula I:



(I)

wherein: ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which optionally may contain 1-3 heteroatoms selected independently from O, N and S; Z is -O-, -NH- or -S-; n is 0, 1, 2, 3, 4 or 5; m is 0, 1, 2 or 3; and R^1 and R^2 are as defined herein, and salts thereof, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals, processes for the preparation of such compounds, pharmaceutical compositions containing a compound of formula I or a pharmaceutically acceptable salt thereof as active ingredient and compounds of formula I. The compounds of formula I and the pharmaceutically acceptable salts thereof inhibit the effects of VEGF, a property of value in the treatment of a number of disease states including cancer and rheumatoid arthritis.